

AVEO PHARMACEUTICALS INC

Form 10-K

March 11, 2011

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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended: December 31, 2010

Or

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the transition period from to

Commission file number: 001-34655

AVEO PHARMACEUTICALS, INC.

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(Exact Name of Registrant as Specified in Its Charter)

Delaware
(State or Other Jurisdiction of
Incorporation or Organization)

04-3581650
(I.R.S. Employer
Identification No.)

75 Sidney Street

Cambridge, Massachusetts 02139

(Address of Principal Executive Offices) (zip code)

Registrant's telephone number, including area code: (617) 299-5000

Securities registered pursuant to Section 12(b) of the Act:

Title of each class
Common Stock, \$.001 par value

Name of each exchange on which registered
NASDAQ Global Market

Securities registered pursuant to Section 12(g) of the Act:

None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☐ No ☒

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes ☐ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405) is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See definitions of "large accelerated filer," "accelerated filer," and "smaller reporting company" in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer ☐

Accelerated filer ☐

Non-accelerated filer ☒ (Do not check if a smaller reporting company)

Smaller reporting company ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☒

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The aggregate market value of the registrant's common stock, \$0.001 par value per share (Common Stock), held by non-affiliates of the registrant, based on the last reported sale price of the Common Stock on the NASDAQ Global Market at the close of business on June 30, 2010, was \$161,865,077. For purposes hereof, shares of Common Stock held by each executive officer and director of the registrant and entities affiliated with such executive officers and directors have been excluded from the foregoing calculation because such persons and entities may be deemed to be affiliates of the registrant. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

The number of shares outstanding of the registrant's Common Stock as of February 28, 2011: 35,788,858

Documents incorporated by reference:

Portions of our definitive proxy statement for our 2011 annual meeting of stockholders are incorporated by reference into Part III of this Annual Report on Form 10-K.

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References to AVEO

Throughout this Form 10-K, the words we, us, our and AVEO refer to AVEO Pharmaceuticals, Inc. and its consolidated subsidiary, and board of directors refers to the board of directors of AVEO Pharmaceuticals, Inc.

Forward-Looking Information

This report contains forward-looking statements regarding our future discovery and development efforts, our collaborations, our future operating results and financial position, our business strategy, and other objectives for future operations. You can identify these forward-looking statements by their use of words such as anticipate, believe, estimate, expect, forecast, intend, plan, project, target, will, and other terms of similar meaning. You also can identify them by the fact that they do not relate strictly to historical or current facts. There are a number of important risks and uncertainties that could cause our actual results to differ materially from those indicated by forward-looking statements. These risks and uncertainties include those inherent in pharmaceutical research and development, such as adverse results in our drug discovery and clinical development activities, decisions made by the U.S. Food and Drug Administration and other regulatory authorities with respect to the development and commercialization of our drug candidates, our ability to obtain, maintain and enforce intellectual property rights for our drug candidates, our dependence on our strategic partners, our ability to obtain any necessary financing to conduct our planned activities, and other risk factors. Please refer to the section entitled Risk Factors in Part I of this report for a description of these risks and uncertainties. Unless required by law, we do not undertake any obligation to publicly update any forward-looking statements.

PART I

ITEM 1. Business Overview

We are a cancer therapeutics company committed to discovering, developing and commercializing targeted cancer therapies to impact patients lives. Our product candidates are directed against important mechanisms, or targets, known or believed to be involved in cancer. Tivozanib, our lead product candidate, which we recently partnered with Astellas Pharma Inc., or Astellas, is designed to provide an optimal blockade of the vascular endothelial growth factor, or VEGF, pathway by inhibiting all three VEGF receptors: VEGF receptors 1, 2 and 3. Our clinical trials of tivozanib to date have demonstrated a favorable safety and efficacy profile for tivozanib. We have completed a successful 272-patient phase 2 clinical trial of tivozanib in patients with advanced renal cell cancer, or RCC. In this trial, we measured, among other things, each patient's progression-free survival, which refers to the period of time that began when a patient entered the clinical trial and ended when either the patient died or the patient's cancer had grown by a specified percentage or spread to a new location in the body. Final data from the trial show the overall median progression-free survival of patients in the phase 2 clinical trial was 11.7 months. In a retrospective analysis of the subset of 176 patients in our phase 2 clinical trial who had the clear cell type of RCC and who had undergone prior removal of their affected kidney, referred to as a nephrectomy, both of which are inclusion criteria for our phase 3 clinical trial of tivozanib, the median progression-free survival was 14.8 months. The most common treatment-related side effects seen in the phase 2 clinical trial were hypertension (44.9%) and dysphonia, or hoarseness of voice (21.7%). Additionally, the incidence of other side effects in the phase 2 clinical trial, which are commonly associated with other VEGF receptor inhibitors, such as diarrhea, rash, mucositis, stomatitis, fatigue, and hand-foot syndrome, was notably low in comparison to clinical trial results of other VEGF receptor inhibitors. Severe (grade 3/4) incidences of these side effects that were considered by the investigator to be possibly related to tivozanib occurred in fewer than two percent of patients. In February 2010, we initiated enrollment in our global, phase 3 clinical trial comparing the efficacy and safety of tivozanib with Nexavar® (sorafenib), an approved therapy, for first-line treatment in RCC, which we refer to as the TIVO-1 study. The TIVO-1 study is being conducted in patients with advanced clear cell RCC who have undergone a prior

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nephrectomy and who have not received any prior VEGF-targeted therapy. In August 2010, we completed enrollment in the TIVO-1 study with 517 patients. We anticipate receiving top-line data from the TIVO-1 study in mid-2011. Nexavar is an oral VEGF receptor inhibitor approved for the treatment of RCC. In its phase 3 clinical trial in patients with advanced clear cell RCC, 94% of whom had undergone a prior nephrectomy, Nexavar demonstrated a median progression-free survival of 5.5 months. Progression-free survival is the primary endpoint in the TIVO-1 study. The TIVO-1 study is designed so that a difference in progression-free survival of three months or more between the treatment arms would be statistically significant.

In addition to the TIVO-1 study, we are evaluating tivozanib in multiple clinical trials including: a completed phase 1b clinical trial in combination with Torisel® (temsirolimus), an approved inhibitor of the receptor known as mammalian target of rapamycin, or mTOR, in patients with advanced RCC; a phase 1b clinical trial in combination with the FOLFOX6 chemotherapy regimen in patients with advanced gastrointestinal cancers, including colorectal cancer; a recently completed phase 1b clinical trial in combination with Taxol® (paclitaxel) in patients with metastatic breast cancers; a phase 1b clinical trial in combination with Xeloda® (capecitabine), an oral chemotherapeutic agent, in patients with breast and colorectal cancers; a completed phase 1b clinical trial as a monotherapy in patients with non-small cell lung cancer; and a phase 2 clinical trial designed to evaluate biomarkers of tivozanib in patients with RCC. In addition, a phase 1 investigator sponsored clinical trial was recently completed in which tivozanib was combined with Afinitor® (everolimus), an approved inhibitor of the mTOR receptor, in patients with advanced colorectal cancer. The phase 2 portion of this investigator sponsored trial combining tivozanib with Afinitor was recently initiated in February 2011 and will enroll patients with refractory metastatic colorectal cancer. We expect that the results of these trials will help to inform our clinical development plans for tivozanib as a monotherapy and in combination with other anti-cancer therapies in multiple cancer indications.

We acquired exclusive rights to develop and commercialize tivozanib worldwide outside of Asia pursuant to a license agreement we entered into with Kirin Brewery Co. Ltd. (now Kyowa Hakko Kirin), or KHK, in 2006. Under the license agreement, we obtained an exclusive license to research, develop, manufacture and commercialize tivozanib, pharmaceutical compositions thereof and associated biomarkers for the diagnosis, prevention and treatment of any and all human diseases and conditions outside of Asia. KHK has retained all rights to tivozanib in Asia. We have obligations to make milestone and royalty payments to KHK. The royalty rates range from the low to mid teens as a percentage of our net sales of tivozanib. We are also obligated to pay a specified percentage of certain amounts we receive from any third party sublicensees, including Astellas. As discussed below under the heading **Recent Developments**, we recently entered into a strategic collaboration with Astellas in which we have agreed to share responsibility, including all profits and losses, with Astellas for continued development and commercialization of tivozanib in North America and Europe. Throughout the rest of the world, outside of North America, Europe and Asia, we granted Astellas an exclusive, royalty-bearing license to develop and commercialize tivozanib.

In addition to tivozanib, we have a pipeline of monoclonal antibodies derived from our proprietary Human Response Platform, a novel method of building preclinical models of human cancer, which are intended to more accurately represent cancer biology in patients. Ficlatusumab (AV-299), our next most advanced product candidate, is an antibody which binds to hepatocyte growth factor, or HGF, thereby blocking its function. Through the use of our Human Response Platform, our scientists have observed that the HGF/c-Met pathway is a significant driver of tumor growth. We have completed a phase 1 clinical trial of ficlatusumab and initiated a phase 2 clinical trial in patients with non-small cell lung cancer in May 2010. In 2007, we entered into an agreement with Merck and Co., Inc., or Merck (through its subsidiary Schering Corporation), under which we granted Merck exclusive worldwide rights to develop and commercialize ficlatusumab. Pursuant to the agreement, Merck funded all research, development and manufacturing expenses, subject to an agreed-upon budget, and under which Merck was obligated to pay development milestones to us, and, as applicable, royalties on product sales. On September 28, 2010, we received notice from Merck of termination of the collaboration agreement effective as of December 27, 2010, at which point we became responsible for the performance and funding of all future research, development, manufacturing and commercialization activities for ficlatusumab.

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We have also identified a number of other promising targets for the development of novel cancer therapeutics using our Human Response Platform. We have preclinical antibody discovery programs underway focusing on targets that appear to be important drivers of tumor growth, including our third clinical candidate AV-203, which targets the ErbB3 receptor (partnered with Biogen Idec, Inc., or Biogen Idec), as well as programs directed toward the RON receptor, the Notch receptors and the Fibroblast Growth Factor receptors.

Our Human Response Platform was designed to overcome many of the limitations of traditional approaches to modeling human cancer. The traditional method of modeling human cancer uses a model referred to as a xenograft. A xenograft model is created by adapting cells from a human tumor to grow in a petri dish, and then injecting these cells in a mouse, where they grow into tumors. However, the resulting tumors differ from the original tumor in important respects, and, accordingly, xenograft models are often poor predictors of the success of cancer drugs in human clinical trials. In our Human Response Platform, we use patented genetic engineering techniques to grow populations of spontaneous tumors in animals containing human-relevant, cancer-causing mutations and tumor variation akin to what is seen in populations of human tumors. Because we believe that these populations of tumors better replicate what is seen in human cancer, we believe that our Human Response Platform provides us with unique insights into cancer biology and mechanisms of drug response and resistance, and represents a significant improvement over traditional approaches. We are utilizing this Human Response Platform alone and with our strategic partners to (i) identify and validate target genes which drive tumor growth, (ii) evaluate drugs which can block the function of these targets and (iii) identify biomarkers, which are indicators of drug response and resistance in patients, in an effort to evaluate which patients are most likely to respond favorably to treatment with such drugs.

Recent Developments

On February 16, 2011, we entered into a collaboration and license agreement with Astellas in connection with which we and Astellas will develop and commercialize tivozanib for the treatment of a broad range of cancers, including RCC and breast and colorectal cancers. Under the terms of the collaboration agreement with Astellas, we will share responsibility with Astellas for continued development and commercialization of tivozanib in North America and in Europe. Throughout the rest of the world (other than North America and Europe, and excluding Asia where KHK has retained all development and commercialization rights), which we refer to as the royalty territory, Astellas has an exclusive, royalty-bearing license to develop and commercialize tivozanib. The terms of the collaboration agreement with Astellas are subject to our obligations to KHK under the license agreement entered into with KHK in 2006.

We will have lead responsibility for formulating the commercialization strategy for North America under the joint commercialization plan, with each of us and Astellas responsible for conducting fifty percent (50%) of the sales efforts and medical affairs activities in North America. Astellas will have lead responsibility for commercialization activities in Europe under the joint commercialization plan and we will be responsible for conducting fifty percent (50%) of the medical affairs activities in the major European countries. All costs associated with each party's conduct of development and commercialization activities in North America and Europe, and any resulting profits or losses, will be shared equally between the parties.

Under the collaboration agreement, we received an initial cash payment of \$125 million, comprised of a \$75 million license fee and \$50 million in research and development funding. We expect to retain net proceeds of approximately \$96 million of the initial cash payment from Astellas, after payments to KHK and strategic, legal and financial advisors. We are also eligible to receive from Astellas an aggregate of approximately \$1.3 billion in potential milestone payments relating to development and commercialization milestones for tivozanib. In addition, if tivozanib is successfully developed and launched in the royalty territory, Astellas will be required to pay to us tiered, double digit royalties on net sales of tivozanib in the royalty territory, if any, subject to offsets under certain circumstances. We are required to pay to KHK a specified percentage of milestones and royalties we may receive from Astellas in connection with Astellas' development and commercialization activities in Europe and the royalty territory.

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Product Pipeline

We are seeking to develop multiple new drugs that target important mechanisms known or believed to be involved in cancer. These drugs include our lead drug candidate, tivozanib, a small molecule oral cancer drug, designed to prevent tumor growth by inhibiting angiogenesis, as well as monoclonal antibodies against HGF and ErbB3. We also are developing a pipeline of earlier stage, novel antibodies that are designed to target mechanisms which we believe to be important in cancer. Our drug discovery and development activities are supported by our Human Response Platform.

The chart below summarizes our current product candidates and their stages of development and planned development.

Tivozanib: Triple VEGF Receptor Inhibitor

VEGF Pathway Inhibitors in Tumor Angiogenesis

The formation of new blood vessels, known as angiogenesis, is required to support certain important natural processes such as embryonic development, reproduction and wound healing. Angiogenesis also plays an important role in cancer progression and the spread of tumors within the body, or metastasis. Tumors cannot grow beyond a small size in the absence of the formation of new blood vessels. Tumors use these vessels to obtain oxygen and nutrients, both of which are required to sustain tumor growth, and to remove toxic waste products that result from rapid metabolism. In addition, new vessels in the tumor provide a way for tumor cells to enter the circulation and to spread to other organs.

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Cancer cells and associated tumor tissue secrete a variety of protein activators, or growth factors, that bind to receptors and promote angiogenesis. Growth factors that bind to specific receptors are known as ligands for those receptors. Vascular endothelial growth factor, or VEGF, stimulates angiogenesis and is required for the maintenance of new blood vessels. Most tumors produce various forms of VEGF and other ligands which bind to the three VEGF receptors, VEGFR1, 2 and 3. The VEGF receptors are found predominantly on the surface of normal vascular endothelial cells. The secretion of these ligands attracts normal endothelial cells to the tumor site where they are stimulated to proliferate and form new blood vessels that feed the tumor.

Each of the three VEGF receptors has been shown to play a distinct and critical role in angiogenesis. Drugs designed to inhibit the VEGF pathway may be directed either to one or more ligands of the receptors, or to the VEGF receptors themselves. Because there are multiple ligands that can bind to the three VEGF receptors and stimulate angiogenesis, products that block only one of these ligands may result in an incomplete blockade of the VEGF pathway. Similarly, receptor-targeted drugs that fail to effectively block all three of the VEGF receptors may also result in an incomplete blockade of the VEGF pathway.

Because essentially all solid tumors require angiogenesis to progress beyond microscopic size, anti-angiogenesis drugs have demonstrated benefit in a wide variety of tumor types. Current therapies targeting the VEGF pathway have been approved in many tumor types, including colon, lung, breast, kidney, liver and brain cancers. In many of these cancers, other than kidney, liver and brain cancers, VEGF pathway inhibitors have demonstrated meaningful efficacy only when given in combination with other drugs; therefore, the opportunity for VEGF pathway inhibitors is most significant for those agents that can be safely combined with other anti-cancer agents.

We believe that the optimal approach to inhibiting the VEGF pathway is through an oral drug that provides optimal blockage of the VEGF pathway by potently and selectively inhibiting all three VEGF receptors. Each of the currently approved VEGF receptor inhibitors has significant side effects when administered alone, and studies have shown that it is challenging to administer these drugs in combination with other anti-cancer agents at their full dose and schedule due to overlapping toxicities. Each of the currently available VEGF receptor inhibitors has one or more drawbacks, including: (i) a lack of adequate potency, which may necessitate high dosage levels in order to sufficiently block all three VEGF receptors; (ii) a lack of selectivity, which may result in off-target side effects due to unintended impact on other biological targets; and, (iii) a short duration of inhibition, which may necessitate dosing more than once per day and may not ensure continuous inhibition of the VEGF pathway.

Despite the various challenges encountered with the approved VEGF receptor inhibitors, sales of VEGF pathway inhibitor drugs have been estimated to exceed over \$10 billion worldwide in 2010, based on quarterly and annual reports made publicly available by companies marketing such drugs. According to EvaluatePharma® consensus forecasts from equity research analysts, drugs targeting angiogenesis are projected to have sales of more than \$14 billion by 2014. Currently approved VEGF pathway inhibitors include Avastin® (bevacizumab), an antibody that blocks only one of the ligands for the VEGF receptors, and Nexavar® (sorafenib), Sutent® (sunitinib) and Votrient® (pazopanib), each of which are small molecule drugs that target the VEGF receptors, but that also bind to a number of other targets with varying potency.

We believe there is a significant unmet need for a new, oral VEGF pathway inhibitor that is designed to provide optimal blockade of all three VEGF receptors, which is more tolerable, which can be more easily combined with other anti-cancer drugs and which can maintain continuous inhibition of the pathway with a convenient dosing regimen.

Potential Advantages of Tivozanib

The potential advantages of tivozanib include a high potency and selectivity profile, which we believe is the basis for the favorable efficacy and safety profile observed in the clinical trials of tivozanib to date. We believe

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that this favorable efficacy and safety profile may allow tivozanib to be successfully used as a monotherapy and to be more readily combined with other anti-cancer agents. Coupled with a convenient dosing regimen, we believe these advantages may differentiate tivozanib from currently marketed and in-development VEGF receptor inhibitors, and may allow tivozanib to fulfill an unmet need in the anti-angiogenesis market.

Potency. Based on published preclinical data to date of marketed products or compounds in clinical development that target the VEGF receptors, we believe that tivozanib is the most potent inhibitor of all three VEGF receptors and that tivozanib provides the most comprehensive blockade of the VEGF pathway. Tivozanib is administered at a dose of 1.5 mg per day. In contrast, the daily dose of the other approved VEGF receptor inhibitors ranges from 50 mg per day to 800 mg per day. Because tivozanib's high potency allows it to be administered at a low dose, patients who take tivozanib have less drug circulating in their body.

Selectivity. Tivozanib more selectively inhibits all three VEGF receptors than it does any other target in the body. This selectivity for the VEGF receptors has the potential to confer two important advantages:

Tolerability. In the clinical trials of tivozanib to date, we have observed low rates of unintended side effects, referred to as off-target toxicities, with hypertension and dysphonia being the most commonly reported side effects in patients. The occurrence of hypertension and dysphonia are driven by inhibition of the VEGF pathway, and suggest that the pathway has been substantially inhibited. Hypertension associated with tivozanib can usually be managed using standard anti-hypertensive drugs, and both hypertension and dysphonia have been manageable and reversible in our clinical trials. As a result, in the phase 2 clinical trial of tivozanib, dose reductions due to side effects were required by 8% of patients, treatment interruptions due to side effects were required by 4% of patients and study discontinuation due to side effects were required by 9% of patients.

In contrast, many of the existing drugs that act by inhibiting the VEGF pathway also inhibit targets in other pathways, which can cause off-target toxicities. Sutent, Nexavar and Votrient, all relatively non-selective VEGF inhibitors, more potently inhibit other targets than they do the VEGF receptors. For example, Sutent and Votrient more potently inhibit the receptor known as c-Kit and Nexavar more potently inhibits the protein known as raf. The most commonly reported toxicities for Sutent and Nexavar are fatigue, rash and diarrhea, and a common toxicity for Votrient is diarrhea. Votrient has also been associated with severe, and sometimes fatal, liver toxicity. These drugs have high rates of a number of other side effects that can be very difficult for patients to tolerate, including: mucositis, a painful inflammation and ulceration of the mucous membranes lining the digestive tract; stomatitis, an inflammation of the mucous lining of the mouth, including the cheeks, gums, tongue, lips, throat and roof or floor of the mouth; and hand-foot syndrome, a blistering, burning, swelling and tenderness on the soles of the feet and palms of the hands that can interfere with a patient's ability to walk and/or use his or her hands. Sutent, Nexavar and Votrient can also cause myelosuppression, which refers to a decrease in the production of blood cells, resulting in both anemia and neutropenia. Anemia is a decrease in the number of red blood cells, which carry oxygen, and neutropenia is a decrease in the number of certain white blood cells, which fight infection.

None of these side effects are believed to be associated with inhibition of the VEGF pathway and, therefore, are considered off-target toxicities. These side effects can be difficult to manage, and result in high rates of dose reductions and discontinuations, as well as a reduced quality of life for patients. In clinical trials, more than 30% of patients receiving Sutent, more than 13% of patients receiving Nexavar and more than 40% of patients receiving Votrient have required dose reductions, and more than 35% of patients receiving Sutent, more than 20% of patients receiving Nexavar and more than 30% of patients receiving Votrient have required dose interruptions.

Combinability. While the approved VEGF pathway inhibitors have demonstrated improvements in outcomes in the patients with cancers they are used to treat, we believe an opportunity exists for significantly improved outcomes through the use of rational combinations of VEGF pathway inhibitors with other anti-cancer therapies. Because of the potency and selectivity of tivozanib, we believe that it

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has the potential to be more readily combined with other anti-cancer drugs at full dose and schedule, and therefore has the potential to significantly improve anti-cancer activity and clinical outcomes. In contrast, combining other anti-cancer drugs, each of which carries with it its own toxicity profile, can lead to high levels of side effects when administered at full dose, or the dose administered when the drugs are used alone, and schedule of dose administration, which can make the combination unsafe or difficult for patients to tolerate. For example, in a phase 1 clinical trial designed to test the safety and efficacy of Sutent in combination with Torisel, another drug approved to treat RCC, the trial had to be halted due to high levels of rash and thrombocytopenia, or an abnormal drop in blood cell count, resulting from this combination. This high toxicity level was observed despite both agents being administered at doses well below the standard doses that are used when administered alone. Similarly, in a phase 2 clinical trial in breast cancer patients designed to test the safety and efficacy of Nexavar in combination with Xeloda, a drug approved for the treatment of breast cancer, patients demonstrated clinical benefit from the combination, however, more than 40% of patients developed grade 3 hand-foot syndrome, which is the highest grade of hand-foot syndrome (there is no grade 4 or grade 5 for this side effect). Hand-foot syndrome is a serious skin reaction that interferes with patients' ability to conduct the normal activities of daily living.

We have commenced the following phase 1b clinical trials testing tivozanib in combination with other anti-cancer agents in multiple cancer types, including RCC, breast and gastrointestinal cancer:

In our recently completed phase 1b clinical trial evaluating the combination of tivozanib with Torisel in patients with RCC, tivozanib and Torisel were both administered at full dose and schedule. Preliminary data from the clinical trial presented in February 2011 indicate that the combination has been well-tolerated and resulted in disease control, defined as stable disease or tumor shrinkage, in 22 out of 28 evaluable patients (79%), with eight patients (29%) experiencing partial responses, which means the patients had a reduction in the sum of the longest diameter of the tumor, or the sum of all tumors, of at least 30% as compared to the longest diameters of the tumor(s) measured when the patient entered the trial.

In our ongoing phase 1b clinical trial evaluating the combination of tivozanib with FOLFOX6, a standard chemotherapy regimen, in patients with gastrointestinal cancers, including colorectal cancer, both tivozanib and FOLFOX6 have been administered at full dose and schedule. Preliminary data from the clinical trial presented in November 2010 indicate that the combination has been well-tolerated and resulted in disease control in 14 of 17 evaluable patients (82%), with six of 17 patients (35%) experiencing partial responses.

In our recently completed phase 1b clinical trial evaluating the combination of tivozanib with Taxol in patients with metastatic breast cancer, both tivozanib and Taxol have been administered at full dose and schedule. Preliminary data from the clinical trial presented in December 2010 indicate that the combination has been well-tolerated and resulted in disease control of at least 24 weeks in eight of 18 evaluable patients (44%), with five of 18 patients (28%) experiencing partial responses.

We are also evaluating two all-oral combinations of tivozanib and other cancer agents, including a combination of tivozanib with Xeloda in a phase 1b clinical trial in patients with breast and colorectal cancer, and a phase 1 investigator sponsored clinical trial in which tivozanib was combined with Afinitor in patients with advanced colorectal cancer, which was recently completed. The phase 2 portion of the trial was commenced in February 2011 and will enroll patients with refractory metastatic colorectal cancer.

Dosing Regimen. In clinical trials, levels of tivozanib in a patient's blood have been maintained for a prolonged period following a single dose, which allows for convenient, once-a-day dosing. Tivozanib has demonstrated an approximate four and a half day half-life, meaning the time it takes for the concentration of a drug in circulation to be reduced by one-half. Drugs with a short half-life may not sufficiently maintain blockade

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of the VEGF receptors throughout the course of therapy, resulting in the potential for patients to experience a rebound effect, which can worsen their condition. For this reason, it is important to maintain sufficient levels of drug in the patient throughout the course of therapy. Because tivozanib has demonstrated a long half-life, we believe it maintains a more complete blockade of the relevant receptors and, accordingly, we dose tivozanib on a convenient, one-capsule, once-per-day schedule.

Renal Cell Cancer

Overview. We completed a 272-patient phase 2 clinical trial of tivozanib in advanced RCC in August of 2010. Final results from this trial show the overall median progression-free survival of patients was 11.7 months. In a retrospective analysis of the subset of 176 patients in our phase 2 clinical trial who had the clear cell type of RCC and who had undergone a prior nephrectomy, both of which are inclusion criteria for our phase 3 clinical trial of tivozanib, the median progression-free survival was 14.8 months. The most common treatment-related side effects seen in the phase 2 clinical trial were hypertension (44.9%) and dysphonia (21.7%). Additionally, the incidence of side effects in the phase 2 clinical trial, which are commonly associated with other VEGF receptor inhibitors, such as diarrhea, rash, mucositis, stomatitis, fatigue, and hand-foot syndrome, was notably low in comparison to clinical trial results of other VEGF receptor inhibitors. Severe (grade 3/4) incidences of these side effects that were considered by the investigator to be possibly related to tivozanib occurred in fewer than two percent of patients. Tivozanib was well-tolerated by patients and relatively few patients needed to discontinue or reduce their dose of tivozanib. In August 2010, we completed enrollment of our phase 3 clinical trial for tivozanib in patients with advanced clear cell RCC who have undergone a prior nephrectomy and who have not received any prior VEGF-targeted therapy. We anticipate receiving top-line data from this registration trial in mid-2011. Based on the data we have received from clinical trials conducted to date, we believe that tivozanib may offer a unique therapeutic alternative for the first-line treatment of advanced RCC.

Market Opportunity. Based on an epidemiology study reported in the Surveillance Epidemiology and End Results (SEER) Cancer Statistics Review conducted by the National Cancer Institute (NCI) (published in 2007), more than 200,000 new cases of kidney cancer will have been diagnosed in the world in 2010, and new cases of kidney cancer have been increasing steadily for the past 65 years. The NCI reports that there will have been more than 60,000 new cases of kidney cancer in the United States in 2010. According to a review article by R. Motzer et al. in the New England Journal of Medicine from 1996, RCC accounts for approximately 90% of all malignant kidney tumors. We estimate, based on publicly-available information, including 2010 quarterly and annual reports made publicly available by companies that market drugs approved for RCC, that the current worldwide RCC market for prescription drugs is over \$1.8 billion, with agents targeting the VEGF pathway representing over 80% of sales. The market is expected to expand significantly over the next ten years, driven by an increased incidence of RCC, an increased use of frontline therapy as more tolerable agents are developed and an increased use of later-stage therapy as more treatment options become available.

Current Diagnosis and Treatments. The diagnosis of RCC is generally made by examination of a tumor biopsy under a microscope. Evaluation of the visual appearance of the tumor cells by a pathologist allows classification of RCC into clear cell or non-clear cell types. In general, patients with clear cell RCC, approximately 80% of all RCC diagnoses according to a 2006 article by N. Nakaigawa et al, in Cancer Research, tend to have a more favorable prognosis than patients with non-clear cell RCC. The initial treatment for most patients with both clear cell and non-clear cell RCC is surgical removal of the tumor, usually requiring removal of the affected kidney, or nephrectomy, if that is technically feasible. Patients who undergo a nephrectomy tend to have a better prognosis than patients who do not undergo a nephrectomy. Patients whose tumors have metastasized to other organs or whose tumors cannot be removed surgically are considered to have advanced RCC. Advanced RCC is highly resistant to chemotherapy. The standard of care for advanced RCC is treatment with one of the recently approved drugs that inhibit the VEGF pathway, including the oral drugs Sutent, Nexavar and Votrient as well as the injectable product Avastin. Although none of these drugs have been compared head-to-head in phase 3 clinical trials, Sutent, Nexavar, Votrient and Avastin (when administered in combination with alpha interferon) have all demonstrated improvements in progression-free survival in clear cell RCC

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patients compared to placebo or interferon. The reported progression-free survival in the treatment arms of the phase 3 clinical trials of these drugs in patients with advanced clear cell RCC is 11.0 months for Sutent, 5.5 months for Nexavar, 9.2 months for Votrient and 10.2 months for Avastin when Avastin is given in combination with interferon. In these trials, the percent of patients who had undergone a prior nephrectomy was 91% for Sutent, 94% for Nexavar, 89% for Votrient and 85% for Avastin. Torisel and Afinitor, drugs which target mTOR, have also been approved in RCC. In their respective phase 3 clinical trials, the reported median progression-free survival for Torisel was 5.5 months in patients with poor-prognosis RCC, and the reported median progression-free survival for Afinitor in patients who had progressed despite prior treatment with a VEGF receptor inhibitor was 4.9 months.

Despite the efficacy of the approved oral VEGF pathway inhibitors, these drugs are also associated with significant side effects such as neutropenia, fatigue, diarrhea, hand-foot syndrome, mucositis, stomatitis and abnormalities in liver function. A significant number of patients in the phase 3 clinical trials for each of these drugs required a reduction or discontinuation of their therapy due to these side effects. Although these drugs were not tested head-to-head in their respective phase 3 clinical trials, the reported frequency of dose reductions from the phase 3 clinical trials of these drugs in patients with advanced RCC is 32% for Sutent, 13% for Nexavar and 42% for Votrient. The reported frequency of dose interruptions due to adverse events in the phase 3 clinical trials of these drugs in patients with advanced RCC is 38% for Sutent, 21% for Nexavar and 36% for Votrient.

The Tivozanib Opportunity. We believe there is unmet need for an RCC therapy that demonstrates significant efficacy while having a safety profile that will allow patients to remain on drug while maintaining a good quality of life. Added potential may exist for a selective VEGF pathway inhibitor that could be combined with other anti-cancer agents having a different mechanism of action, as VEGF pathway inhibitors are often most effective when administered in combination with other anti-cancer agents.

Clinical Trials

Standard Response Evaluation Criteria in Solid Tumors (version 1.0), or RECIST, defines disease progression and tumor response based on changes of a set of target tumor lesions identified when the patient enters the trial, which we refer to as baseline. A 20% or greater increase in the sum of the longest diameters in the target lesions compared to the smallest sum of the longest diameter recorded since the treatment started, unequivocal progression in non-target lesions or the appearance of a new lesion, is defined as disease progression. A reduction of at least 30% in the sum of the longest diameters of the target lesion as compared to baseline is defined as a partial response. A complete disappearance of target and non-target lesions, and the normalization of any tumor markers, constitutes a complete response. Both partial and complete responses must be confirmed by repeat assessments at least four weeks after the partial or complete response was first documented. Stable disease refers to patients who exhibit neither response nor disease progression. Objective response rate is typically defined as the sum of the partial and complete response rates.

Phase 1 Clinical Trials. In 2007, we completed a phase 1 clinical trial of tivozanib in 41 cancer patients. Results from the phase 1 clinical trial showed that patients were able to tolerate tivozanib at a dose of 1.5 mg/day given continuously for 4 weeks followed by a 2 week rest period, and that toxicities were reversible upon stopping treatment. The primary dose-limiting toxicity identified in the phase 1 clinical trial was hypertension, which is a common side effect of VEGF inhibitors and is considered an on-target side effect resulting from the blockade of the VEGF receptors. Hypertension was treated with standard anti-hypertensive agents such as calcium channel blockers or angiotensin converting enzyme inhibitors.

In the phase 1 clinical trial, nine of 41 patients had RCC, and all nine patients experienced clinical benefit from tivozanib. Two of these patients had a partial response, according to RECIST criteria, including one patient whose partial response lasted for over two years. The remaining seven RCC patients had stable disease lasting for at least two months. Stable disease was also observed in patients with other types of solid tumors including colorectal cancer, where four out of 10 patients who had progressed after prior chemotherapy demonstrated

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stable disease lasting for approximately six months during treatment with tivozanib. One patient with an acinar cell tumor of the pancreas that had progressed after prior treatment with gemcitabine received tivozanib for over two years with stable disease. Given the promising activity observed in the phase 1 clinical trial, we decided to move forward with the development of tivozanib in multiple solid tumors, with RCC being the leading program.

Phase 2 Clinical Trial. In 2007, we began a phase 2 clinical trial of tivozanib in patients with advanced RCC. This clinical trial was conducted under an Investigational New Drug application submitted to the FDA, and 272 patients were enrolled between October 2007 and July 2008 at sites in Russia, the Ukraine and India. To be eligible for the clinical trial, patients could not have received any prior VEGF-targeted therapies. Results from the phase 1 clinical trial showed that patients were able to tolerate tivozanib at a dose of 1.5 mg/day given continuously for four weeks followed by a two week rest period, but in order to minimize the rest period during which patients are off treatment, the dosing regimen for the phase 2 clinical trial was changed to three weeks continuous dosing followed by a one week rest period. The trial included patients with both clear cell RCC (83%) and non-clear cell RCC (17%), and 27% of patients had not had a prior nephrectomy. Approximately 54% of patients had not received any other drug treatment for their disease, while the remainder had received one or more prior therapies, but no VEGF pathway inhibitors.

All patients received tivozanib for the first 16 weeks, at which time, based on investigator assessment, patients with $\geq 25\%$ tumor regression continued on tivozanib for the next 12 weeks while patients with $< 25\%$ change from baseline were randomly assigned to tivozanib or placebo in a double-blinded manner for the next 12 weeks. Patients with $\geq 25\%$ increase in tumor size discontinued tivozanib treatment.

The primary endpoints of the trial were (i) the percentage of patients remaining progression-free 12 weeks following random assignment to tivozanib or placebo, (ii) objective response rate after the initial 16 week treatment period and (iii) safety. Secondary endpoints included overall progression-free survival from start of treatment and progression-free survival after random assignment to tivozanib or placebo.

All radiology scans from the study were reviewed, retrospectively, by a single, centralized group of independent radiologists in the United States who were blinded to treatment assignment. All laboratory tests were conducted at a central lab in the United Kingdom. Disease progression and tumor response rates were determined in accordance with RECIST. The data reported in the following paragraph with respect to the percentage of patients remaining progression-free 12 weeks following random assignment as compared to placebo are based on final data from the tivozanib phase 2 clinical trial. Progression-free survival was significantly higher among patients with clear cell RCC (12.4 months) compared to patients with non clear cell RCC (6.7 months). Within the group of 176 patients with clear cell histology and prior nephrectomy, progression-free survival was similar between those patients who were treatment naïve (14.3 months), and those who had received prior therapy with cytokines and/or chemotherapy (15.9 months). There were 51 patients who remained on tivozanib therapy for more than 2 years.

A significantly higher percentage of patients on tivozanib remained progression-free 12 weeks following random assignment as compared to placebo. As assessed by the study investigators, 57% of patients randomized to tivozanib were progression-free compared to 28% of patients randomized to placebo (Figure 1). This difference was statistically significant ($p=0.001$). The median progression-free survival of patients from the 12-week double-blind period was 3.3 months for patients randomized to the placebo treatment arm and 10.3 months for patients randomized to the tivozanib treatment arm. The median was calculated based on data from the phase 2 clinical trial using a standard statistical procedure known as a Kaplan-Meier analysis. The vertical tick marks of the graphs below represent points during the clinical trial at which one or more patients were removed from the data analysis either because the patient was on treatment and still responding at the time of the data cut-off or because the patient withdrew from the clinical trial due to reasons other than disease progression or because the patient was randomized to placebo.

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Figure 1: Progression-Free Survival by Independent Radiological Review Assessments (Censored Dropouts, Intended to Treat (ITT) Population Excluding Subjects with Progressive Disease Prior to Randomization)

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Figure 2 shows the probability of a patient remaining alive without tumor progression while in the tivozanib phase 2 clinical trial. The overall median progression-free survival of patients in the phase 2 clinical trial was 11.7 months.

Figure 2: Progression-Free Survival by Independent Radiological Review Assessments (Censored Dropouts, All Treated Population)

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In the subset of 176 patients in the phase 2 clinical trial who had clear cell RCC and who had undergone a prior nephrectomy, both of which are inclusion criteria for our phase 3 clinical trial of tivozanib, the median progression-free survival was 14.8 months, calculated retrospectively using a Kaplan-Meier analysis, as shown in Figure 3.

Figure 3: Progression-Free Survival Throughout the Study by Independent Radiological Review Assessments (Censored Dropouts, All Treated Population, Subjects with Clear Cell Histology and Nephrectomy)

Approximately 84% of patients who received tivozanib therapy and had at least one post-baseline CT scan in the phase 2 clinical trial experienced some degree of tumor shrinkage while on therapy. By independent radiological assessment, 24.3% of patients who received tivozanib demonstrated a confirmed objective response. There was one (0.4%) confirmed complete response, and 65 (23.9%) confirmed partial responses as measured by independent radiological assessment. In patients with clear cell RCC who had undergone a prior nephrectomy, 29.5% had a confirmed objective response as measured by independent radiological assessment. The confirmed responses include one confirmed complete response and 51 confirmed partial responses. Per RECIST, confirmed responses are defined as responses that are confirmed by a repeat assessment that is performed at least four weeks after the criteria for response are first met.

The maximum percent change relative to baseline in the sum of the longest diameters at each tumor assessment for the 238 patients in the phase 2 clinical trial with at least one post-baseline CT scan is presented as a waterfall graph in Figure 4. The graph below shows the change in tumor size for each of these patients in the phase 2 clinical trial. Each vertical bar in the graph represents the percent change from the time when the patient entered the clinical trial (baseline) until the maximum change was observed for that patient. The changes in tumor size are based on independent radiological assessment.

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Figure 4: Waterfall Plot: Maximum Change in Tumor Size Throughout the Study (All Treated Population)

The most common treatment-related adverse events seen in our phase 2 clinical trial of tivozanib were combined hypertension, which includes the adverse events of hypertension, blood pressure increased, essential hypertension, and hypertensive crisis (122 subjects, 44.9%), dysphonia (59 subjects, 21.7%), diarrhea (33 subjects, 12.1%), and asthenia or weakness (28 subjects, 10.3%). Hypertension is well established as an effect of inhibition of the VEGF pathway. Dysphonia has been associated with a variety of VEGF inhibitors but the causal mechanism is not as well established as it is with respect to hypertension.

Of the 272 patients enrolled in the clinical trial, 25 patients discontinued tivozanib due to an adverse event, 22 patients had a dose reduction due to an adverse event, and 11 patients had a dose interruption due to an adverse event.

Table 1 lists drug-related adverse events seen in >5% of patients and includes the number of patients in which these drug-related adverse events were seen. Grade 1 adverse events are characterized as mild, Grade 2 adverse events are moderate, Grade 3 adverse events are severe, Grade 4 adverse events are life-threatening, and Grade 5 adverse events are fatal.

The incidence of mucositis, stomatitis and hand-foot syndrome were less than 5%, with less than 1% Grade 3 or Grade 4 events reported. No Grade 5 events occurred.

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System Organ Class Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	All Grades Total
Combined Hypertension	15(5.5%)	74(27.2%)	31(11.4%)	1(0.4%)	0(0%)	122(44.9%)
Dysphonia	55(20.2%)	4(1.5%)	0(0%)	0(0%)	0(0%)	59(21.7%)
Diarrhea	21(7.7%)	7(2.6%)	5(1.8%)	0(0%)	0(0%)	33(12.1%)
Asthenia	7(2.6%)	14(5.1%)	7(2.6%)	0(0%)	0(0%)	28(10.3%)
Fatigue	9(3.3%)	8(2.9%)	5(1.8%)	0(0%)	0(0%)	22(8.1%)
Dyspnoea	6(2.2%)	7(2.6%)	3(1.1%)	0(0%)	0(0%)	16(5.9%)

Combined hypertension includes the following: hypertension, blood pressure increased, essential hypertension, and hypertensive crisis. Subjects could be counted more than once if they had more than one of these side effects, but were counted only one time for the total combined hypertension class.

Phase 3 Clinical Trial. Based on the results of the phase 2 clinical trial of tivozanib and following discussions we have had with the FDA and European Medicines Agency, or EMA, we initiated a phase 3 clinical trial in patients with advanced clear cell RCC who have undergone a prior nephrectomy in December 2009, referred to as the TIVO-1 study. We commenced enrollment in this clinical trial in February 2010, and completed enrollment in August 2010. The TIVO-1 study enrolled 517 patients in 15 countries, including the United States, Canada, Europe, South America and India.

The TIVO-1 study is a global, phase 3, randomized clinical trial comparing the efficacy and safety of tivozanib with Nexavar® (sorafenib) for first-line treatment in RCC. The TIVO-1 study is being conducted in patients with advanced clear cell RCC who have undergone a prior nephrectomy, and who are treatment-naïve or have received no more than one prior regimen of immunotherapy or chemotherapy, with no prior VEGF-targeted therapy. The primary endpoint for the trial is progression-free survival. Based on our discussions with the FDA and the EMA, we set the number of patients to be enrolled in the clinical trial based on standard statistical assumptions and an assumed difference in progression-free survival of three months or more between the treatment arms would be statistically significant. Secondary endpoints include overall survival, objective response rate, duration of response, which is a measure of the time from when a patient's tumors have shrunk until they resume their growth in size, and quality of life, as measured from questionnaires completed by the patient that provide information about symptoms and the impact of the cancer on a patient's daily life activities. Results from the TIVO-1 study, together with results from our already completed phase 2 clinical trial, will form the basis for registration applications to be submitted to the U.S. and European regulatory agencies for tivozanib's approval in advanced RCC.

Nexavar was approved in the United States in December 2005 as the first VEGF receptor inhibitor for the treatment of advanced RCC. Nexavar received marketing authorization by the European Commission in July 2006 for the treatment of patients with advanced RCC who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy. In the phase 3 clinical trial of Nexavar, patients with advanced clear cell RCC, 94% of whom had undergone a prior nephrectomy, treated with Nexavar had a median progression-free survival of 5.5 months and patients treated with placebo had a median progression-free survival of 2.8 months. Following discussions with both the FDA and EMA, both agencies indicated that Nexavar is an acceptable choice as the active comparator in the TIVO-1 study.

In the TIVO-1 study, patients have been randomized in approximately equal numbers to treatment with tivozanib or Nexavar. Patients randomized to the tivozanib treatment arm receive tivozanib on the same dose and schedule that was well tolerated in our phase 2 clinical trial of tivozanib. Patients randomized to the Nexavar treatment arm receive the approved dose of Nexavar, which is 400 mg twice a day. Patients randomized to the tivozanib treatment arm who develop documented disease progression will be discontinued from the clinical trial. Patients randomized to the Nexavar treatment arm who develop documented disease progression will be discontinued from the clinical trial and will be given the option to receive tivozanib by enrolling in a separate

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long-term treatment protocol. In order to meet FDA standards for assessing results in phase 3 trials, all radiology scans will be assessed by a single, centralized group of independent radiology reviewers in the United States who will be blinded to the assigned treatment. There can be no assurance that the efficacy and safety profile seen in prior clinical trials of Nexavar and of tivozanib will be reproduced in the TIVO-1 study.

In addition to the TIVO-1 study, we are conducting, or plan to conduct, or will seek waivers from conducting, a variety of other clinical trials that would support a New Drug Application, or NDA, including a mass balance study, a food effect study, a thorough QTc study, drug-drug interaction studies, special population studies, and a pediatric study. We are also conducting additional toxicology studies in non-human primates and rodents, which will be included in our registration application.

Tivozanib Combination Therapy

We believe tivozanib's favorable efficacy and safety profile increases its potential to be combined with other anti-cancer agents in a manner that may produce better clinical outcomes. As a result, we have a number of clinical trials underway that are designed to test tivozanib in combination with other drugs and chemotherapies in multiple solid tumor types. We are also utilizing our Human Response Platform to help identify rational drug combinations and patient populations most likely to be responsive to these combination therapies. We expect that the results of these clinical trials, together with the results of our ongoing research efforts, will help to inform our clinical development plans for tivozanib in additional indications.

Renal Cell Cancer. Based on preclinical studies we have conducted using our Human Response Platform, we believe that the combination of tivozanib and mTOR inhibitors may have enhanced anti-tumor activity in patients with RCC. We recently completed a phase 1b clinical trial of tivozanib in combination with Torisel, an injectable mTOR inhibitor, in patients with advanced clear cell RCC who have failed up to one prior VEGF-targeted therapy. Torisel was approved by the FDA for the treatment of advanced RCC in 2007, and is considered a standard of care for treatment of patients with poor-prognosis RCC.

Clinical trials have shown that Sutent cannot be used in combination with Torisel due to severe toxicities. A phase 1 clinical trial testing the combination of Sutent and Torisel was discontinued when two out of the first three patients treated in the first cohort with less than full doses of each drug (15 mg of Torisel and 25 mg of Sutent) developed serious dose-limiting toxicities such as rash and thrombocytopenia.

Nexavar has also had a significant challenge combining with Torisel at full doses due to a variety of dose-limiting toxicities. The only approved VEGF pathway inhibitor that we are aware of that is currently being developed in combination with Torisel at full doses is Avastin. The preliminary data using this combination showed a high rate of tumor shrinkage in patients with RCC. However, the results presented at the ASCO Annual Meeting in 2010 for the TORAVA trial, which tested the combination of Avastin and Torisel in patients with RCC, showed substantial toxicity with this combination.

While no other oral VEGF receptor inhibitor has demonstrated that it can be safely combined with Torisel at full dose and schedule, to date, the results of our recently completed phase 1b clinical trial indicate that tivozanib may be able to be used safely in combination with Torisel at full recommended dose and schedule. Preliminary data from the clinical trial reported in February 2011 indicate that the combination has been well-tolerated and resulted in disease control in 22 out of 28 evaluable patients (79%), with eight patients (29%) experiencing partial responses as assessed by RECIST.

Breast Cancer. We believe that tivozanib can provide an improved therapy for women diagnosed with breast cancer. In 2010, approximately 207,000 women will have been diagnosed with invasive breast cancer, and 40,000 women will have died from breast cancer, in the United States, according to the American Cancer Society. Currently available chemotherapy and hormonal therapies have significantly enhanced the survival of women diagnosed with breast cancer; however metastatic breast cancer remains an incurable disease.

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Avastin was approved by the FDA in 2008 for the treatment of metastatic breast cancer. In December 2010, the FDA moved to revoke Avastin's approval in this indication based on recent clinical trial data indicating that the benefits of Avastin may be outweighed by dangerous side effects. The drug remains approved in metastatic breast cancer in the U.S. while Avastin's manufacturer, Roche-Genentech, has appealed the FDA's decision. Despite the recent data, European regulators have decided to retain the approval of Avastin for advanced breast cancer when used in combination with paclitaxel.

In addition, previously presented phase 2 clinical trial data show that Nexavar when combined with Xeloda, an oral chemotherapy approved in breast cancer, improved outcomes in patients over Xeloda alone. However, overlapping toxicities have resulted in numerous side effects, including more than 40% of patients experiencing the highest grade of hand-foot syndrome, Grade 3.

We recently completed a phase 1b clinical trial of tivozanib in combination with a standard dose of Taxol in patients with metastatic breast cancer. Preliminary data from the clinical trial reported in December 2010 indicate that the combination has been well-tolerated and resulted in disease control of at least 24 weeks in eight of 18 evaluable patients (44%), with five of 18 patients (28%) experiencing partial responses.

Based on tivozanib's favorable toxicity profile, and minimal off-target toxicities with tivozanib monotherapy in clinical trials to date, we believe that tivozanib has the potential to be safely combined with Xeloda. Accordingly, we have initiated a phase 1b clinical trial evaluating the combination of tivozanib with Xeloda. The primary objectives of the trial are to determine the safety, tolerability and maximum tolerated dose of tivozanib when administered in combination with Xeloda. In the next component of this trial, we plan to enroll patients with locally advanced or metastatic breast or colorectal cancer to further evaluate safety and activity of this combination in these tumor types. We anticipate that the results of this trial will guide our future decisions regarding potential additional trials of this combination regimen.

Colorectal Cancer. We believe that tivozanib has the potential to improve the treatment of colorectal cancer when used in combination with standard of care chemotherapy or other targeted drugs. According to the American Cancer Society, in the United States in 2010, approximately 143,000 patients will have been diagnosed with colorectal cancer, and 51,000 patients will have died from this disease. Despite recent advances in chemotherapy, the American Cancer Society also reports that less than 10% of patients with metastatic colorectal cancer survive beyond 5 years. Therefore, there is a critical need for new and more effective treatments for colorectal cancer. Based on recent clinical trials, Avastin in combination with chemotherapy has become the standard of care for metastatic colorectal cancer. These studies have demonstrated that the VEGF pathway is important in colorectal cancer. We believe more potent inhibitors of the pathway, such as tivozanib, have the potential to improve therapy for this disease.

In 2008, we initiated a phase 1b clinical trial of tivozanib in combination with FOLFOX6, a standard chemotherapy regimen, in patients with gastrointestinal cancers, including colorectal cancer. This clinical trial has shown that tivozanib can be safely administered at full dose (1.5 mg) and schedule in combination with full dose FOLFOX6 chemotherapy. Preliminary data from the clinical trial reported in November 2010 indicate that the combination has been well-tolerated and resulted in disease control in 14 of 17 evaluable patients (82%), with six of 17 patients (35%) experiencing partial responses as assessed by RECIST. This clinical trial is currently enrolling patients for an expanded assessment of safety and activity in this patient population.

In November 2010, we initiated a phase 1b clinical trial evaluating an all-oral combination of tivozanib with Xeloda in patients with advanced solid tumors. In the next component of this trial, we plan to enroll patients with locally advanced or metastatic breast or colorectal cancer to further evaluate safety and activity of this combination in these tumor types.

Building on the safety data generated to date in the Torisel combination clinical trial in RCC, we are also interested in exploring the safety and activity of tivozanib in combination with an mTOR inhibitor in colorectal

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cancer. A phase 1 investigator sponsored clinical trial was recently completed evaluating the combination of tivozanib with Afinitor, an oral mTOR inhibitor approved for the treatment of RCC, in patients with advanced colorectal cancer. The phase 2 portion of this all-oral clinical trial combining tivozanib and Afinitor commenced in February 2011 and will enroll patients with refractory metastatic colorectal cancer. If this clinical trial is successful, we believe that an all-oral regimen comprising a VEGF pathway inhibitor and an mTOR inhibitor would be an attractive drug combination worthy of further development in colorectal cancer.

Non-small Cell Lung Cancer. We believe that tivozanib could also provide an improved treatment for patients with advanced non-small cell lung cancer, or NSCLC. Lung cancer is the most deadly cancer in men and women, with approximately 223,000 new cases and 157,000 deaths in the United States in 2010, according to the American Cancer Society. Chemotherapy has shown modest activity in NSCLC and advanced lung cancer remains an incurable disease. Avastin, approved by the FDA for use in NSCLC in combination with chemotherapy, and various small molecular VEGF receptor inhibitors have demonstrated modest single-agent activity in lung cancer.

We recently completed a phase 1 clinical trial of tivozanib monotherapy in patients with advanced NSCLC, and we are in the process of aggregating and analyzing the data from this trial. This clinical trial is designed to test a continuous dosing regimen of tivozanib. We expect that the results will provide preliminary indications of activity in this cancer and further inform our development strategy for tivozanib.

Orphan Drug Designation

In June of 2010, the EMA granted orphan medicinal product designation for tivozanib for RCC. According to the EMA, tivozanib was awarded the designation based on the prevalence of RCC among people in the European Union; the life-threatening nature of the disease, particularly for those with advanced or metastatic RCC; and the assumption that tivozanib may provide significant benefit for patients with RCC, and may be more potent and specific than existing treatments with similar mechanism of action as supported by preliminary clinical results. Companies granted orphan medicinal product designation by the EMA receive, among several other benefits, market exclusivity in the European Union for ten years following market authorization. Demonstration of quality, safety and efficacy is necessary before a designated orphan medicinal product can be granted a marketing authorization.

Ficlatuzumab (AV-299): Anti Hepatocyte Growth Factor (HGF) Antibody

Through the use of our Human Response Platform, our scientists have identified the HGF/c-Met pathway as a significant driver of tumor growth. HGF is a protein that circulates in the blood and binds to and activates a receptor called c-Met. HGF is the sole known ligand of c-Met receptor. Activation of c-Met is believed to be important in normal processes in embryonic development and wound healing. Activation of c-Met, however, is also believed to trigger many activities that are involved in cancer development and metastasis. Altered HGF/c-Met signaling is observed in many tumors including lung, bladder, breast, gastric, ovarian, prostate, colorectal, head and neck, certain sarcomas and in multiple myeloma and leukemias. There are no approved therapies that target the HGF/c-Met pathway.

Less than two years after scientists characterized the importance of the HGF/c-Met pathway, we identified our ficlatuzumab antibody, a potent and functional inhibitor of HGF. In preclinical models, ficlatuzumab has demonstrated an ability to inhibit the growth of many different tumors, including lung and colon tumors, glioblastomas and multiple myeloma. In preclinical studies of ficlatuzumab, we have also shown that ficlatuzumab has additive efficacy when given in combination with other approved anti-cancer agents such as Tarceva® (erlotinib), Erbitux® (cetuximab) and Temodar® (temozolomide). In preclinical studies conducted by us, ficlatuzumab was more effective at inhibiting tumor growth (at the dose tested) than AMG-102 and TAK-701, the other anti-HGF antibodies currently in clinical development. Clinical trials will need to be conducted in order to determine whether the differences observed in these preclinical studies will contribute to greater efficacy in patients.

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Preclinical and clinical observations suggest that increased HGF and/or c-Met receptor amplification may confer resistance to epidermal growth factor receptor (EGFR) inhibitors. Recently, encouraging phase 2 clinical data were reported at the 2010 ASCO Annual Meeting with a third party small molecule c-Met inhibitor in combination with an EGFR tyrosine kinase inhibitor (TKI) in patients with advanced, refractory NSCLC. Additionally, phase 2 clinical data were reported at the 2010 35th Congress of the European Society for Medical Oncology (ESMO) with a third party antibody to the c-Met receptor in combination with an EGFR TKI in patients with advanced, refractory NSCLC. These phase 2 clinical data demonstrated encouraging trends in progression-free survival and overall survival for a subset of patients treated with this antibody. Collectively, we believe that these data signal the potential patient benefit from combination therapy of an EGFR TKI and an inhibitor of the HGF/c-Met pathway.

In 2008, we commenced a phase 1 clinical trial of ficlatuzumab, which has completed enrollment, in patients with a variety of solid tumors to establish the safety, tolerability, pharmacokinetics, maximum tolerated dose and the recommended phase 2 clinical trial dose of ficlatuzumab as a monotherapy, and to determine the safety, tolerability, and maximum tolerated dose of ficlatuzumab in combination with Tarceva, an approved EGFR inhibitor. A total of 24 patients received ficlatuzumab as a monotherapy, and 13 patients were dosed with ficlatuzumab in combination with Tarceva. The phase 1 clinical trial showed good tolerability with no dose limiting toxicities up to the highest dose tested, 20mg/kg, for the monotherapy cohorts. One patient dosed with ficlatuzumab, 20mg/kg, in combination with Tarceva, experienced inflammation of the mucous lining of the mouth. The most frequently observed adverse events were mild fatigue, hypokalemia, or low blood potassium, tissue swelling, also referred to as edema, and nausea. A preliminary review of response data for the monotherapy cohorts showed that 11 out of 24 patients enrolled in the phase 1 clinical trial experienced stable disease lasting for 12 weeks or more, as shown in the chart below. Review of response data for the ficlatuzumab/Tarceva cohort is underway.

We are also conducting a phase 1 clinical trial in cancer patients with liver metastases in order to evaluate the activity of ficlatuzumab in HGF pathway activation in metastatic tumors.

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In May 2010, we commenced a phase 2 clinical trial testing a combination of ficlatuzumab with Iressa® (gefitinib), an EGFR inhibitor, randomized 1:1 versus Iressa alone in patients with newly diagnosed non-small-cell lung cancer. Patients who demonstrate disease progression during treatment with Iressa alone will have the opportunity to be treated with ficlatuzumab in combination with Iressa provided that safety is maintained and the patient continues to meet trial eligibility criteria. This 170-patient, randomized clinical trial, which is being conducted in Asia, will study response rate and progression-free survival in two distinct patient subsets: those with activating EGFR mutations and those with wild-type EGFR. We expect to receive top-line efficacy data from the phase 2 trial in 2012.

We are also using our Human Response Platform to identify tumor types and patient populations most likely to be responsive to ficlatuzumab therapy. There are very few traditional preclinical models that are driven by HGF/c-Met. Consequently, we have utilized our proprietary technology to develop novel model systems that can be used preclinically to give insights into the best clinical settings in which to test a novel inhibitor of the pathway. We believe that these preclinical models will provide us with an advantage over other competitive programs.

In March 2007, we entered into a collaboration agreement with Merck (through its subsidiary Schering Corporation) under which we granted Merck worldwide rights to develop and commercialize ficlatuzumab. Pursuant to the terms of the collaboration agreement, Merck funded all research, development and manufacturing expenses, subject to an agreed-upon budget, was responsible for manufacturing ficlatuzumab for clinical use and was required to pay us development milestones and royalties on the sale of ficlatuzumab. On September 28, 2010, we received notice from Merck of termination of the collaboration agreement effective as of December 27, 2010, at which point we became responsible for the performance and funding of all future research, development, manufacturing and commercialization activities for ficlatuzumab.

AV-203: Anti ErbB3 Antibody Program

Through the use of our Human Response Platform, our scientists have highlighted the importance of the ErbB3 receptor in tumor growth. ErbB3 belongs to a family of four proteins that also includes EGFR and HER2.

Both EGFR and HER2 have been implicated in promoting the growth of significant numbers of tumors, particularly in breast and lung cancers. Drugs blocking the activity of EGFR have demonstrated clinical benefit in lung, colon and head and neck cancers while drugs targeting HER2 show clinical benefit in the treatment of HER2 overexpressing breast and gastric cancers.

ErbB3 is significantly over-expressed in many human breast, ovarian, prostate, colorectal, pancreatic, gastric, and head and neck cancers and its overexpression generally correlates with poor prognosis. It has also been implicated in resistance to certain drugs which target EGFR in lung cancer and with resistance to radiotherapy. In addition, while the anti-HER2 antibody Herceptin has been very successful in treating many breast tumors that express HER2, HER2 is only overexpressed (HER2 positive) in roughly 25% of breast cancer and as many as 60% of HER2 positive patients do not respond, as reported in a 2007 Herceptin review by C.A. Hudis published in *The New England Journal of Medicine*. Because ErbB3 preferentially binds with HER2, we believe that breast cancer patients who do not respond well to anti-HER2 therapy might benefit from drug combinations with an anti-ErbB3 antibody.

Through our discovery efforts, we have identified antibodies that have been shown to be potent and selective inhibitors of ErbB3 in preclinical studies. In preclinical testing, these antibodies have significantly inhibited the growth of a number of different tumors, including breast, prostate and pancreatic cancers. We selected AV-203 as our lead development candidate in March 2010, and have commenced process development for manufacturing of this candidate in preparation for preclinical studies and human clinical trials. We have not yet submitted to the FDA an investigational new drug application for AV-203, and anticipate initiating phase 1 development with AV-203 in 2012.

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In March 2009, we granted Biogen Idec an exclusive option to obtain rights to co-develop (with us) and commercialize our ErbB3-targeted antibodies for the potential treatment and diagnosis of cancer and other diseases outside of the United States, Canada and Mexico. Under the agreement, we are responsible for developing ErbB3 antibodies through completion of the first phase 2 clinical trial designed in a manner that, if successful, will generate data sufficient to support advancement to a phase 3 clinical trial.

Within a specified time period after we complete the phase 2 clinical trial and deliver to Biogen Idec a detailed data package containing the results thereof, Biogen Idec may elect to obtain (1) a co-exclusive (with us) worldwide license under our relevant intellectual property to develop and manufacture ErbB3 antibody products, and (2) an exclusive license under our relevant intellectual property to commercialize ErbB3 antibody products in all countries in the world other than in the United States, Canada and Mexico. We retain the exclusive right to commercialize ErbB3 antibody products in the United States, Canada and Mexico. Until completion of the first phase 2 clinical trial, we are solely responsible for the research, development, and manufacturing of ErbB3 antibody(ies) pursuant to a written work plan meeting specific pre-agreed guidelines. We are solely responsible for all expenses incurred through completion of the first phase 2 clinical trial. If Biogen Idec exercises its option to obtain exclusive commercialization rights to ErbB3 products in its territory, then we will be solely responsible, subject to a mutually agreed development plan, budget and the oversight of a joint development committee, for the global development of ErbB3 antibody products, except that Biogen Idec will be solely responsible for ErbB3 antibody product development activities that relate solely to the Biogen Idec territory. We and Biogen Idec will share global development costs (including manufacturing costs to support development) for ErbB3 antibody products equally, except that Biogen Idec will be solely responsible for all development costs associated solely with the development of ErbB3 antibody products for its territory, and we will be solely responsible for all development costs associated solely with the development of ErbB3 antibody products for the United States, Canada and Mexico.

Other Antibody Pipeline Programs

In addition to the HGF/c-Met pathway and ErbB3, we have utilized our Human Response Platform to identify a number of other targets that appear to be potent drivers of tumor growth. We have further evaluated the involvement of these targets in the development of human cancers using available human cancer databases. Targets with the ability to drive tumor growth in our tumor models and with frequent genetic alterations in human cancers were selected as targets for our next generation of antibody drug discovery programs. The targets we have focused on to date are the Notch receptors, FGF receptors and the RON receptor, as more fully described below.

Notch Program. Genetic screens conducted using our Human Response Platform have demonstrated that activation of the Notch signaling pathway is a potent driver of tumor growth and confirmed its important role in tumor formation, or tumorigenesis. The Notch receptors are a family of four receptors on the surface of cells, Notch1-4, whose activity has been shown to play important roles in normal stem cell function and in multiple aspects of tumor biology.

Notch signaling is also thought to be important for the maintenance of cancer stem cell populations in tumors. Cancer stem cells are thought to represent a distinct cell population within the tumor contributing to tumorigenesis. Cancer stem cells may cause tumor metastasis and relapse following anti-tumor treatments by regenerating the tumor tissue. Eradication of cancer stem cells may lead to increased survival in cancer patients. We intend to use our Notch specific antibodies to investigate the role of Notch signaling in the maintenance of cancer stem cells. We believe that this effort may lead to the development of a novel therapeutic regimen that specifically targets cancer stem cell populations.

The goal of our Notch drug discovery efforts is to identify specific inhibitory antibodies to Notch1, Notch2 and Notch3 that prevent ligand binding and activation of the receptors. The program has generated functional inhibitory antibodies against the Notch1 and Notch3 receptors. Our team has demonstrated proof of concept with our lead Notch1 antibody candidate in preclinical models of angiogenesis and preclinical testing is ongoing. In

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these preclinical models, our Notch1 antibody shows no evidence of the gastro-intestinal toxicity that has limited the clinical development of other Notch inhibitors. As part of our ongoing Notch1 research, we are also currently evaluating the impact of prolonged, genetic inhibition of Notch1 which recent publications have suggested may result in vascular tumors and hemorrhage in the liver in research conducted in mice.

We are utilizing our Human Response Platform to investigate the context in which Notch inhibition, either alone or in combination with tivozanib, would have the greatest efficacy. Because the blockade of Notch1 signaling results in a potent inhibition of angiogenesis by a mechanism which differs from VEGF inhibition, we believe that blockade of both pathways simultaneously might increase the efficacy of anti-angiogenesis therapy. We are also exploring preclinical models to determine which tumors might be uniquely dependent on Notch1 function for survival as another mechanism of action for the drug. Our scientists have identified the HeyL protein as a potential biomarker that predicts that a significant subset of tumors driven by the mutant Ras oncogene may depend on Notch function. Oncogenes are genes that, when mutated, help turn normal cells into cancer cells. Specifically, high levels of HeyL in colon and pancreatic cell lines that carry a mutated form of Ras correlate with the sensitivity of these tumors to Notch pathway inhibitors. In June 2009, we were granted a U.S. patent on a method of identifying cancer tissue likely to be sensitive or resistant to treatment with an inhibitor of Notch receptor activation.

Fibroblast Growth Factor Program. Fibroblast growth factors, or FGFs, and their receptors, FGFR1-4, represent a signaling network that plays an important role in the regulation of cell growth, survival, differentiation and angiogenesis. Work in our Human Response Platform identified FGF ligands and receptors as powerful drivers of tumor growth in a variety of tumor models and implicated the activation of the pathway in tumor development. Increasing amounts of human genetic and genomic data also point to the alteration of this pathway in the development of a number of different types of human cancers.

Recently, the human Cancer Genome Sequencing project identified the FGF/FGFR pathway as the most frequently altered signaling pathway in human cancers. Similar studies demonstrated that FGF pathway activation may not only play a role in tumor development but also may be implicated in the development of drug resistance. Different tumors and tumor types exhibit varying profiles of FGF pathway alterations; therefore, targeting individual FGF receptors may have different therapeutic applications.

Certain FGF ligands have been shown to have pro-angiogenic activity and may act synergistically with VEGF to amplify tumor angiogenesis. The upregulation of FGF pathway activity in response to anti-VEGF therapy is thought to play an important role in the development of resistance to VEGF inhibition, suggesting that the combination of FGF and VEGF pathway inhibitors may add to the benefits achievable by targeting VEGF alone.

The goal of our ongoing drug discovery efforts is to identify specific FGFR1, FGFR2, FGFR3 and FGFR4 inhibitory antibodies that prevent activation of these receptors. We will evaluate the activity of candidate antibodies in specific target-driven tumor models created using our Human Response Platform.

RON Program. RON is a receptor closely related to c-Met which is the receptor for HGF, the target of ficlatuzumab. Similarly, the Macrophage Stimulating Protein, which activates RON, is most closely related to HGF. The activation of RON signaling is believed to trigger many of the same cellular activities as activation of the HGF/c-Met pathway. Like c-Met, RON has been implicated in promoting tumor cell metastasis and invasiveness and, in one preclinical breast cancer model, RON expression in tumor cells dramatically increased their ability and propensity to metastasize to bone.

RON and c-Met are frequently co-expressed in certain tumors. Breast, bladder and colon cancer patients whose tumors have high levels of RON or c-Met have a poor prognosis, and the worst prognosis has been observed in patients in which both receptors were over-expressed.

Our scientists have identified antibodies which can inhibit the growth of RON-driven tumors created through our Human Response Platform. Preclinical testing of these antibodies is ongoing.

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Our Human Response Platform

Our scientific founders, Ronald A. DePinho, M.D. and Lynda Chin, M.D., both of the Harvard Medical School and the Dana Farber Cancer Institute, Tyler Jacks, Ph.D., of the Massachusetts Institute of Technology, and Raju Kucherlapati, Ph.D., of the Harvard Medical School, leaders in the field of cancer modeling and cancer genetics, believed that traditional preclinical cancer models were poorly predictive of drug responses in patients and that work from their various laboratories indicated that substantially better models of cancer could be developed. Accessing key intellectual property and insights from our founders, we have created a series of unique genetically engineered models of cancer, as well as proprietary ways of analyzing complex gene expression data to better translate such data from our models to human patient populations. These innovations help to address three key issues in cancer drug discovery and clinical development:

Target Identification and Validation: Identifying and validating which of the many candidate cancer causing genes are most important to tumor growth.

Drug Discovery: Enabling the development of tumor models driven by the target gene of interest to facilitate the evaluation of drug candidates directed against the target, and the selection of the most promising candidate.

Biomarker Identification: Enabling the identification of genetic markers, or biomarkers, which may help identify patients who are more likely to be responsive or resistant to such drugs by leveraging the naturally occurring genetic variation in our cancer models and their divergent sensitivity to anti-cancer drugs.

We believe that our platform provides unique insights into cancer biology that may provide us and our strategic partners with a competitive advantage in all phases of cancer drug discovery and development. To date, Merck and OSI have entered into agreements with us to utilize our Human Response Platform.

Scientific Background

Cancer is a disease caused by genetic mutations that accumulate in cells over the lifetime of an individual that can ultimately result in the unrestrained growth of the altered cells and their invasion into surrounding normal tissues. Cancer causing mutations arise at random within a cell, which then undergoes a selective process where any mutation that provides the cell with an increased ability to grow and survive is retained. It is estimated that at least a dozen different mutations are required to transform a normal cell into a cancerous one. Even within specific types of cancer that all carry certain powerful cancer causing mutations, there are multiple combinations of additional mutations present such that each individual tumor is slightly different.

During the last 20 years, many of the mutations which promote cancer in people have been identified from human tumors. These have generally fallen into two classes: oncogene activating mutations and tumor suppressor gene mutations. Oncogene activating mutations function to promote cell growth. By analogy to driving a car, oncogene activating mutations act much like pushing the accelerator to the floor, giving a permanent signal to promote cell growth. Examples of these mutations include mutations in EGFR, HER2 and K-Ras. Tumor suppressor gene mutations inactivate mechanisms which turn off cell growth. Elimination of tumor suppressor gene function is analogous to cutting the brake lines in the car: mechanisms to stop the growth of the cell are gone. When a single cell collects an oncogene activating mutation and a tumor suppressor gene mutation, it is not yet transformed into a cancer cell but it is well on its way. Research has shown that introduction of these two types of mutations in many different cell types is sufficient to induce tumor formation over time. During this time, additional spontaneous mutations arise to complete the transformation of the normal cell into a full blown cancer cell capable of unlimited growth.

Limitations of Existing Cancer Models

Researchers use cancer models to help identify targets for new cancer drugs, to help screen the best drugs directed against such targets and to help identify which cancer patients are most likely to benefit from treatment with such drugs. For these reasons, cancer models which most accurately recreate the attributes of cancer in patients are important to increase the likelihood of successfully developing new safe and effective cancer drugs.

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For the past several decades the standard models used by cancer researchers have been xenograft models. A xenograft model is created by adapting cells from a human tumor to grow in a petri dish. These cells are then injected under the skin of a mouse, where they grow into a tumor. Researchers can then test drugs to see if they can inhibit growth of the resulting tumors without causing unacceptable side effects.

This approach has several limitations. First, the process of adapting the human tumor cells to grow in a petri dish results in further unintended changes to the tumor cells that cause them to change in ways that do not reflect the original tumor from which they came. Second, because of the differences between human cells and mouse cells, the human cells are not able to interact in a natural way with the cells in the surrounding tissues. Finally, because there are relatively few of these xenograft models for each human tumor type, it is difficult to understand the reasons why some of these models respond to certain drugs and others do not.

Xenograft models are often poor predictors of the success of cancer drugs in human clinical trials and there is a substantial need in oncology for preclinical models that better replicate human cancer. For example, as reported in a 2006 article by K. Garber in *Journal of National Cancer Institute*, only 3.8% of patients in phase 1 clinical cancer drug trials show a significant clinical response, whereas most of these drugs have been shown to work in xenograft models in mice.

Our Human Response Platform

We were founded with the goal of developing a fundamentally new kind of cancer model designed to overcome many of the limitations of traditional xenograft models, and thereby improve the probability of success in developing new cancer drugs. We utilize these novel models to identify and validate target genes which drive tumor growth, to identify drugs which can block the function of these targets, and to identify patients who are most likely to respond favorably to treatment with such drugs. We have used these models to advance drugs in our pipeline and in collaboration with our strategic partners such as Merck, OSI and Biogen Idec. Our cancer models, together with the various techniques we have developed to use these models to aid in the discovery and development of new cancer drugs, are collectively referred to as our Human Response Platform. Key components of our Human Response Platform are covered by issued patents or pending patent applications.

Our Novel Approach to Modeling Human Cancer

We begin the development of our genetically-engineered tumor models by introducing a human oncogene into mouse stem cells in which we have inactivated the function of a tumor suppressor gene. As in human cancer, these are the two key elements which are necessary to begin the process of a cell becoming cancerous. The oncogene is introduced in a manner which allows us to control its expression we can direct in which tissue it will be expressed (e.g., breast or lung or colon), and we can turn it on by adding a simple non-toxic chemical to the animal's drinking water. We refer to this genetic engineering process as the inducible oncogene approach, as it allows the researcher to control whether or when to induce, or turn on, the oncogene.

Originally, we used this inducible oncogene approach in germ line transgenic mice, which we licensed from the Dana Farber Cancer Institute when we were founded, in which the oncogene is expressed in all of the cells of the animal. However, recognizing that in naturally occurring human tumors oncogenes are only activated in a subset of the cells of the body, we subsequently developed an alternate method which are called chimeric mice, in which the oncogene is only activated in a subset of the cells of the animal. This makes it a more realistic model than a germ line transgenic model in which the entire animal is made up of genetically modified cells.

In our patented method of making chimeric mouse models, the key starting mutations that will allow them to develop into cancerous cells are introduced directly into the stem cells. Then, we inject the stem cells into 3-day old mouse embryos, alongside normal cells, and implant the embryos into mice. When the mice are born, we turn on the expression of the oncogene. Animals do not develop tumors right away, but expression of the oncogene begins a process whereby the engineered cells begin to accumulate additional genetic alterations

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randomly over a period of months. Eventually, most animals develop tumors in the tissue where we have directed the oncogene to be expressed. Importantly, although the initial driving oncogene is the same in every tumor, the additional mutations which accumulate are different from animal to animal, just as would be the case in a human population.

The power and versatility of our mouse model platform is greatly enhanced by our patented method of making chimeric mouse models. Prior to our invention of this patented method, every time a different chimeric model was desired, a germ line transgenic mouse containing all the desired genetic modifications had to be produced by a lengthy process that included at least one, and often several, rounds of breeding, in order to obtain the embryonic stem cells necessary to make the desired chimeric model. For a biopharmaceutical company frequently needing to produce new chimeric models containing different mutations, producing each new chimeric model through the conventional breeding process would be prohibitively time-consuming. We addressed this problem by greatly improving the speed of chimeric model production. In our patented method, it is no longer necessary to do mouse breeding every time a new chimeric model is produced. Instead, all the desired genetic modifications are assembled directly in an individual mouse embryonic stem cell, which is then injected into a mouse embryo. This reduces the time required to produce each new chimeric mouse model by as much as one year. We believe that this ability to produce new chimeric models in a commercially meaningful time frame is an important advance in the state of the art.

In addition to this patented method of making new tumor models, we have also developed a model of human breast cancer in which we have applied many of these same features to genetically modified human breast tissue. This Human-in-Mouse model is created by first isolating normal human breast tissue from surgical specimens, genetically modifying it to express oncogenes and then introducing the modified tissue into specially-engineered mice. The modified breast tissue first grows into normal breast tissue, but then rapidly develops into human breast tumors while growing in the mouse breast tissue. To our knowledge, this is the first and only preclinical model in which normal human breast tissue has been engineered to develop into spontaneous breast tumors in a mouse.

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Advantages of Our Cancer Models

We believe that our novel cancer models have a number of unique advantages over traditional xenografts and other methods of developing cancer models used in many academic settings. First, because the tumors grow naturally in the animals, the normal interactions between tumors and the tissues around them, including blood vessels, are preserved. This is not the case in traditional xenografts, where human tumor cells are implanted into mice, and certain of the important cellular signals sent by the growing human tumor may not be recognized by the surrounding mouse cells. Second, as is the case in human cancer, the cancer cells grow alongside normal cells, whereas in many other cancer models, all of the cells of the animal contain the cancer-causing mutations. Third, because of the switch that we introduce into our models, we can turn on the cancer-causing mutations after the animals are born, replicating what is seen in many human cancers. In many other models, these mutations are on before the animals are born, and interfere with their normal embryonic development. Finally, because tumors in our model develop spontaneously after introduction of the initial cancer causing mutations, we can develop populations of tumors that exhibit differences in genetic backgrounds, again much more akin to what is seen in a population of human tumors.

Use of Our Models in Target Discovery and Validation

In a proprietary method called the MaSS screen, we turn off the inducible oncogene driving the growth of the tumors in our models. We then activate other genes in the tumor cells to see if the tumor cells grow with the driving oncogene turned off. This allows us to screen for genes capable of replacing the function of a known oncogene. Such genes are potential new targets for anti-cancer drugs. The MaSS screen technique is protected by issued patents exclusively licensed to us by the Dana-Farber Cancer Institute.

We have conducted MaSS screens in multiple tumor models we developed in different tumor types with different genetic backgrounds. These screens identified many genes important in tumor formation. The most common pathway identified in our screens has been the HGF/c-Met pathway, and this observation triggered the initiation of our program to develop antibodies against HGF (our ficlatuzumab program). Numerous other pathways have also been identified in our screens, including ErbB3, Notch and FGF, all of which are now the basis of certain of our ongoing antibody discovery programs.

The data from all of the screens performed to date are routinely re-evaluated and compared with data coming from other sources, such as mutations identified in the human Cancer Genome Sequencing project. Many target genes originally identified in the screen are poorly understood these targets become more interesting as targets as new data about their function becomes available. This now very large data set provided the basis of our target discovery strategic partnerships with both Merck and OSI. In the case of OSI, scientists from our company and OSI have reevaluated our target data base with a goal of finding novel targets possibly involved in the transition of a tumor cell to a more aggressive phase, where the original epithelial tumor cell becomes more mesenchymal like more invasive and able to survive passage through the blood stream the so-called epithelial-mesenchymal transition.

Use of Our Models in Drug Discovery

One of the significant challenges in drug discovery can often be identifying preclinical models that are driven by a particular target of interest. Human xenografts, for example, may be driven by multiple targets, and have many other limitations. For this reason, developing tumor models that are known to be driven by a particular target can be an important drug discovery tool for identifying the most potent drug candidates against that target.

Because the driving oncogene in our models can be turned on and off, we can turn off the oncogene and replace it with other genes of interest. For example, in the cells of a breast tumor that was originally driven by HER2, we can turn off the HER2 gene, and replace it with EGFR, another important oncogene. When we do so, the tumors that arise from those cells are no longer sensitive to drugs that inhibit HER2, but are sensitive to drugs

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that inhibit EGFR. These tumors provide an excellent system for studying the relative ability of different EGFR inhibitors, either antibodies or small molecules, to affect tumor growth driven by EGFR. This is a powerful preclinical model for ranking the efficacy of different compounds and an example of our patented directed complementation technique. Frequently, similar systems are not available for new targets or newly discovered mutated forms of existing targets, and, accordingly, this technology provides a convenient way of rapidly generating new drug testing systems. We have used this approach to support our antibody drug discovery and development programs.

Use of Our Models in Biomarker Identification

Because each of the tumors that develops in our models accumulates random genetic mutations independently, populations of tumors in our models exhibit a significant degree of genetic heterogeneity. Consequently, the tumors that develop in our models, like human tumor populations, typically exhibit variation in response to anti-cancer drugs. The tumors in our models have been studied extensively for genetic characteristics, providing an opportunity to correlate the genetic makeup, or genetic context, of each tumor with its relative sensitivity or resistance to a given anti-cancer drug. By understanding the genetic context of tumors that respond to particular drugs, we hope to identify genetic markers, or biomarkers, that can be measured in patients prior to treatment to select or predict which tumors, tumor subtype, or patient subsets are most likely to respond to a given anti-cancer drug. We are using this approach to identify potential biomarkers for our pipeline drugs and it will be important to demonstrate that the biomarkers we identify translate into clinical benefit in humans.

In our tivozanib program, we have used our Human Response Platform to identify candidate biomarkers that are expected to help to predict responsiveness to tivozanib therapy. Because most traditional xenograft models are highly sensitive to VEGF pathway inhibitors (in fact, more sensitive than human tumors in patients), such models are not useful for identifying biomarkers. In contrast, because we are able to identify both responsive and resistant tumors in our models and compare the genetic makeup of the tumors, our Human Response Platform is useful for identifying candidate biomarkers. We have two issued United States patents on different biomarker tests, or similar tests, for identifying patients likely to be sensitive or resistant to treatment with tivozanib. We intend to use these candidate biomarker tests in clinical trials of tivozanib.

Recently, we initiated patient enrollment in a multi-center phase 2 exploratory biomarker study of tivozanib in patients with RCC. A key primary objective of the study is to evaluate biomarkers in blood and archived tissue samples and their correlation with tivozanib clinical activity to further inform the potential future design of rational combinations in RCC, as well as in other cancers.

Similar efforts to identify candidate biomarkers for our other development programs are also underway. For instance, in June 2009, we were granted a U.S. patent on a method of identifying cancer tissue likely to be sensitive or resistant to treatment with an inhibitor of Notch activation.

Competition

The biotechnology and pharmaceutical industries are highly competitive. There are many pharmaceutical companies, biotechnology companies, public and private universities, and research organizations actively engaged in the research and development of products that may be similar to our products. A number of multinational pharmaceutical companies, as well as large biotechnology companies, including Roche Laboratories, Inc., or Roche, Pfizer Inc., or Pfizer, Bayer HealthCare AG, or Bayer, Sanofi-Aventis, US, LLC, Amgen, Inc. and GlaxoSmithKline plc, or GSK, are pursuing the development or are currently marketing pharmaceuticals that target VEGF, HGF and ErbB3, or other oncology pathways on which we are focusing. It is probable that the number of companies seeking to develop products and therapies for the treatment of unmet needs in oncology will increase.

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Many of our competitors, either alone or with their strategic partners, have greater financial, technical and human resources than we do and greater experience in the discovery and development of product candidates, obtaining FDA and other regulatory approvals of products and the commercialization of those products. Accordingly, our competitors may be more successful than we may be in obtaining approval for drugs and achieving widespread market acceptance. Our competitors' drugs may be more effective, or more effectively marketed and sold, than any drug we may commercialize and may render our product candidates obsolete or non-competitive before we can recover the expenses of developing and commercializing any of our product candidates. We anticipate that we will face intense and increasing competition as new drugs enter the market and advanced technologies become available.

Tivozanib Competition

Angiogenesis inhibitors represent a rapidly growing drug category in oncology with 2010 sales estimated to be in excess of \$10.0 billion worldwide, based on 2010 quarterly and annual reports made publicly available by companies marketing such drugs. There are currently four FDA-approved drugs in oncology which target the angiogenesis pathway. Avastin, marketed by Roche, is an infused monoclonal antibody approved in combination with other anti-cancer agents for the treatment of metastatic colorectal cancer, metastatic non-small cell lung cancer, HER2-negative metastatic breast cancer, and advanced RCC. It is also approved as a monotherapy for the treatment of glioblastoma in patients with progressive disease following prior therapy. There are three FDA-approved oral small molecule VEGF receptor inhibitors: Nexavar, marketed by Bayer and Onyx Pharmaceuticals, Inc.; Sutent, marketed by Pfizer; and Votrient, marketed by GSK. These approved drugs are non-specific and target other receptors more potently than the VEGF receptors. Nexavar is approved as a monotherapy for advanced RCC and unresectable hepatocellular cancer. Sutent is approved as a monotherapy for advanced RCC and for gastrointestinal stromal tumors. Votrient is approved as a monotherapy for advanced RCC. Other recently approved agents for the treatment of RCC are Torisel, marketed by Pfizer and Afinitor, marketed by Novartis Pharmaceuticals Corporation, both of which inhibit mTOR.

We are aware of a number of companies that have ongoing programs to develop both small molecules and biologics that target the VEGF pathway. We believe the only other VEGF pathway inhibitor in late-stage development in RCC is Pfizer's AG013736 (axitinib), which was recently reported to have met its primary endpoint in a phase 3 registration clinical trial for the second-line treatment of advanced RCC. Other VEGF pathway inhibitors in late-stage development in other cancer types include Amgen Inc.'s and Takeda Pharmaceutical Company Limited's AMG706 (motesanib), Abbott's ABT-869 (linifanib), AstraZeneca plc's AZD2171 (Recentin, cediranib) and AZD6474 (Zactima, vandetanib), Bayer's BAY-73-4506 (regorafenib), Boehringer Ingelheim International GmbH's BIBF-1120 (intedanib), Bristol-Myers Squibb Company's BMS-582664 (brivanib alaninate), Exelixis Inc.'s XL-184 (cabozantinib), ImClone LLC's IMC-1121b (ramucirumab), Onco Therapy Science Inc.'s OTS-102 (elpamotide) and Regeneron Pharmaceuticals, Inc.'s and Sanofi-Aventis US LLC's aflibercept.

Ficlatuzumab Competition

We believe the products in development targeting HGF consist of Amgen's AMG-102 (rilotumumab), currently in phase 2 clinical trials, and Takeda's TAK-701 (HuL2G7, under license from Galaxy Biotech, LLC), currently in phase 1 clinical trials.

Other clinical-stage drugs which target the HGF/c-Met pathway include Roche's MetMab (5D5 Fab), ArQule, Inc.'s / Daiichi Sankyo, Inc.'s ARQ-197, MethyGene, Inc.'s MGCD-265, Exelixis' and GSK's XL-880 (foretinib), Incyte Corp.'s and Novartis' INCB-028060, Pfizer's PF-2341066 (crizotinib) and Exelixis' XL-184(cabozantinib).

AV-203 Program Competition

We believe the most direct competitors to our AV-203 program are monoclonal antibodies that specifically target the ErbB3 receptor, including Merrimack Pharmaceuticals, Inc.'s and Sanofi-Aventis' MM-121, which is

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currently in phase 2 clinical development, and Daiichi Sankyo and Amgen, Inc. s U3-1287 / AMG-888, which is also in phase 2 clinical development. Other clinical-stage competitors include PharmaMar s elisidepsin, Merrimack s MM-111, and AstraZeneca s AZD-8931.

Strategic Partnerships

We have entered into multiple strategic partnerships in which we have granted rights to tivozanib, our antibody candidates and certain aspects of our Human Response Platform. These agreements provide us with a source of cash flow in the form of up-front payments, equity investments, research and development funding, payments upon achievement of specified milestones, and potential royalties from product sales.

Pursuant to the following strategic partnerships entered into as of December 31, 2010, we have acquired rights to products, granted rights to our product candidates, or have utilized, or granted rights to certain elements of, our Human Response Platform:

Strategic Partner	Initial Date of Agreement	Subject Matter	Payments
			Received as of December 31, 2010 ⁽¹⁾⁽²⁾
Kyowa Hakko Kirin	December 2006	Tivozanib ⁽³⁾	N/A
OSI Pharmaceuticals	September 2007	Target and Biomarker Identification	\$ 62.0 million
Biogen Idec	March 2009	AV-203	\$ 55.0 million ⁽⁴⁾
Merck	November 2003	Target Identification	\$ 22.3 million
Merck	August 2005	Biomarker Identification	\$ 6.5 million

(1) Includes up-front payments, equity investments, research and development funding and milestone payments.

(2) The foregoing table does not include receipt of the initial cash payment from Astellas in March 2011 of an aggregate of \$125 million, of which we expect to retain net proceeds of approximately \$96 million, in connection with the execution of a collaboration and license agreement with Astellas.

(3) In December 2006, we in-licensed the rights to our lead product candidate, tivozanib, in all territories of the world, except for Asia.

(4) Includes an equity investment made prior to the initial date of the agreement.

Kyowa Hakko Kirin

In December 2006, we entered into a license agreement with Kirin Brewery Co. Ltd. (now Kyowa Hakko Kirin), which we sometimes refer to as KHK, under which we obtained an exclusive license to research, develop, manufacture and commercialize tivozanib (f/k/a KRN951), pharmaceutical compositions thereof and associated biomarkers. In this description, our references to tivozanib include pharmaceutical compositions thereof and associated biomarkers. Our exclusive license covers all territories in the world, except for Asia. The territory in which we are licensed is referred to as our territory. Kyowa Hakko Kirin has retained rights to tivozanib in Asia, including the People's Republic of China, India and Japan. Under the license agreement, we obtained exclusive rights in our territory under certain Kyowa Hakko Kirin patents, patent applications and know-how related to tivozanib, to research, develop, make, have made, use, import, offer for sale, and sell tivozanib for the diagnosis, prevention and treatment of any and all human diseases and conditions. We have the right to grant sublicenses under the foregoing licensed rights, subject to certain restrictions. In addition, we may, but are not obligated to, apply our Human Response Platform to identify optimal chemotherapy combinations, as well as additional patient populations likely to respond to tivozanib monotherapy and combination therapy. We and Kyowa Hakko Kirin each have access to and can benefit from the other party's clinical data and regulatory filings with respect to tivozanib and biomarkers identified in the conduct of activities under the license agreement.

Under the license agreement, we are obligated to use commercially reasonable efforts to develop and commercialize tivozanib in our territory, including meeting certain specified diligence goals. We also must obtain Kyowa Hakko Kirin's consent if we intend to change the initial indication for which we seek marketing

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approval for tivozanib to an indication other than RCC. Prior to the first anniversary of the first post-marketing approval sale of tivozanib in our territory, neither we nor any of our subsidiaries has the right to clinically develop, seek marketing approval for or commercialize any other product that also works by inhibiting the activity of the VEGF receptor.

Upon entering into the license agreement, we made a cash payment in the amount of \$5.0 million. In March 2010, we made a cash payment in the amount of \$10.0 million in connection with the initial dosing of patients in the TIVO-1 study. In addition, we are required to make certain milestone payments which could total, in the aggregate, \$50.0 million, upon the achievement of specified regulatory milestones. In connection with the execution of our collaboration agreement with Astellas Pharma Inc., or Astellas, discussed below, we are required to pay Kyowa Hakko Kirin a specified percentage of the license fee received from Astellas as well as certain amounts we may receive from Astellas in connection with Astellas' development and commercialization activities outside of North America and Asia related to tivozanib, other than amounts we receive in respect of research and development funding or equity investments, subject to certain limitations. We are also required to pay Kyowa Hakko Kirin tiered royalty payments on net sales we make of tivozanib in North America, which range from the low to mid teens as a percentage of net sales. The royalty rate escalates within this range based on increasing tivozanib sales. Our royalty payment obligations in a particular country in our territory begin on the date of the first commercial sale of tivozanib in that country, and end on the later of 12 years after the date of first commercial sale of tivozanib in that country or the date of the last to expire of the patents covering tivozanib that have been issued in that country.

The license agreement will remain in effect until the expiration of all of our royalty and sublicense revenue obligations to Kyowa Hakko Kirin, determined on a product-by-product and country-by-country basis, unless we elect to terminate the license agreement earlier. If we fail to meet our obligations under the agreement and are unable to cure such failure within specified time periods, Kyowa Hakko Kirin can terminate the agreement, resulting in a loss of our rights to tivozanib and an obligation to assign or license to Kyowa Hakko Kirin any intellectual property or other rights we may have in tivozanib, including our regulatory filings, regulatory approvals, patents and trademarks for tivozanib.

Astellas Pharma Inc.

In February 2011, we entered into a collaboration and license agreement with Astellas and certain of its indirect wholly owned subsidiaries in connection with which we and Astellas will develop and commercialize tivozanib for the treatment of a broad range of cancers, including RCC, and breast and colorectal cancers. Under the terms of the collaboration agreement, we and Astellas will share responsibility for continued development and commercialization of tivozanib in the United States, Mexico and Canada, or North America, and in Europe under the joint development plan and joint commercialization plan, respectively. Throughout the rest of the world, which we refer to as the royalty territory (which excludes North America, Europe and Asia), Astellas has an exclusive, royalty-bearing license to develop and commercialize tivozanib. Our plan to commercialize tivozanib in collaboration with Astellas, as described herein, is subject to our and Astellas' receipt of necessary regulatory approvals from the FDA and foreign regulatory authorities based upon favorable results in clinical trials. There can be no assurance that such approvals will be obtained.

Assuming successful approvals of tivozanib by applicable regulatory agencies, we will hold all marketing authorizations in North America, including any new drug application in the United States, and Astellas will hold all marketing authorizations in the rest of the world, other than Asia.

Assuming successful approvals of tivozanib by applicable regulatory agencies, we, as the lead commercialization party in North America, will have lead responsibility for formulating the commercialization strategy for North America under the joint commercialization plan, with each of us and Astellas responsible for conducting fifty percent (50%) of the sales efforts and medical affairs activities in North America. Astellas will have lead responsibility for commercialization activities in Europe under the joint commercialization plan, and

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we will be responsible for conducting fifty percent (50%) of the medical affairs activities in the major European countries. We have not yet completed our assessment of our accounting for the Astellas arrangement, however, we expect to record all sales of tivozanib in North America, if any, and Astellas will record all sales of tivozanib in Europe, if any. All costs associated with each party's conduct of development and commercialization activities in North America (including any regulatory milestones and royalties associated with tivozanib in North America which may become payable by us to KHK under our license agreement with KHK), and any resulting profits or losses, will be shared equally between the parties. All costs associated with each party's conduct of development and commercialization activities in Europe, and any resulting profits or losses, will be shared equally between the parties. As between the parties, we will remain responsible for complying with our sublicense revenue sharing obligations, if any, to KHK under our license agreement with KHK in connection with the development and commercialization of tivozanib outside of North America.

The collaboration activities in North America and Europe will be governed by a joint steering committee and specified development, medical affairs, manufacturing and commercialization subcommittees, each comprised of an equal number of representatives from each party. The joint steering committee will be responsible for approving, by unanimous consent, the joint development plan and various aspects of the joint commercialization plan for North America and Europe, including commercialization strategy.

We are responsible for manufacturing, through our third party manufacturer, all of Astellas's requirements for tivozanib pursuant to clinical supply and commercial supply agreements with Astellas. However, Astellas will be solely responsible for packaging and labeling with respect to commercial supply of tivozanib for all areas of the world other than North America and Asia. The parties will share equally the manufacturing costs for supply of tivozanib for North America and Europe, and Astellas's manufacturing costs for packaging and labeling with respect to commercial supply of tivozanib for Europe, and Astellas is obligated to pay us a specified fee for supply of tivozanib for the royalty territory.

Each party is obligated to use commercially reasonable efforts to develop and commercialize tivozanib in each of the United States, Mexico and Canada, including the filing of an NDA in the United States to treat patients with RCC, and to develop and commercialize tivozanib in each European country specified in the agreement. Astellas is also obligated to use commercially reasonable efforts to develop and commercialize tivozanib in each country in the royalty territory.

During the term of the agreement, neither party nor its controlled affiliates may commercialize anywhere in North America, Europe or the royalty territory any product that has a specified mechanism of action (as further defined in the collaboration agreement) for any oncology indication, except that Astellas may commercialize specified compounds for hematological cancer. Astellas may also commercialize products (other than tivozanib) in the royalty territory, on a country-by-country basis, upon expiration of the applicable royalty term, and in North America and Europe upon expiration of all valid claims under the licensed patents.

In connection with the agreement, we received an initial cash payment of \$125 million, comprised of a \$75 million license fee and \$50 million in research and development funding, both of which are non-creditable and non-refundable against any amounts due under the collaboration agreement. We expect to retain net proceeds of approximately \$96 million of the initial cash payment from Astellas, after payments to KHK and strategic, legal and financial advisors. We are also eligible to receive an aggregate of approximately \$1.3 billion in potential milestone payments, comprised of (i) up to \$575 million in milestone payments upon achievement of specified clinical development and regulatory milestone events, including up to \$90 million in milestone payments in connection with specified regulatory filings, and receipt of marketing approvals, for tivozanib to treat RCC in the United States and Europe, and (ii) up to \$780 million in milestone payments upon the achievement of specified sales events. In addition, if tivozanib is successfully developed and launched in the royalty territory, Astellas will be required to pay to us tiered, double digit royalties on net sales of tivozanib in the royalty territory, if any, subject to offsets under certain circumstances. We are required to pay to KHK a specified percentage of milestones and royalties we may receive from Astellas in connection with Astellas's development and commercialization activities in Europe and the royalty territory.

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Unless terminated earlier in accordance with its terms, the collaboration agreement with Astellas expires (a) with respect to the royalty territory, on a country by-country basis, upon the latest to occur of: (i) the expiration of the last-to-expire valid claim of an AVEO patent or joint patent covering the composition of tivozanib, (ii) the expiration of the last-to-expire valid claim of an AVEO patent or joint patent covering the use of tivozanib, but only for so long as no generic competition exists in such country, and (iii) twelve years from first commercial sale of tivozanib in such country, and (b) with respect to North America and Europe as a whole, upon the expiration of all payment obligations between the parties related to development and commercialization of tivozanib in North America and Europe. After the second anniversary of the effective date of the collaboration agreement, Astellas has the right to terminate the collaboration agreement, in its entirety or solely with respect to the royalty territory, at any time upon 180 days prior written notice to us. Either party may terminate the collaboration agreement with respect to a specified territory or country as set forth in the collaboration agreement, if the other party fails to cure a material breach related to such territory or country, as applicable. We may also terminate the collaboration agreement in its entirety upon a patent-related challenge by Astellas, its affiliates or sublicensees, if such patent-related challenge is not withdrawn within 30 days following our notice to Astellas of such termination.

OSI Pharmaceuticals

In September 2007, we entered into a collaboration and license agreement with OSI Pharmaceuticals, Inc., or OSI (a wholly owned subsidiary of Astellas US Holding, Inc., a holding company owned by Astellas), which provides for the use of our proprietary *in vivo* models by our scientists at our facilities, use of our bioinformatics tools and other target validation and biomarker research to further develop and advance OSI's small molecule drug discovery and translational research related to cancer and other diseases. Our strategic partnership with OSI is primarily focused on the identification and validation of genes and targets involved in the processes of epithelial-mesenchymal transition, or EMT, or mesenchymal-epithelial transition, or MET, in cancer. EMT/MET processes are of emerging significance in tumor development and disease progression. We are currently working with OSI on the development of proprietary target-driven tumor models for use in target validation, drug screening and biomarker identification to support OSI's drug discovery and development activities. The research program portion of our strategic partnership began in October 2007 and will expire at the end of June 2011 unless the agreement is terminated earlier by either party. Key elements of our strategic partnership with OSI include:

identifying and validating a pre-agreed number of oncology targets for small molecule drug discovery, development and commercialization by OSI;

generating target-driven *in vivo* mouse tumor models for use in drug screening and biomarker validation to support OSI's drug discovery and translational research activities; and

applying our Human Response Platform to identify genetic profiles that correlate with drug response to compounds in certain of OSI's small molecule drug discovery programs.

We are required to devote, and OSI is required to fund, a mutually agreed minimum number of individuals to the research program each year.

Under the terms of our agreement, OSI may, but has no obligation to, elect to obtain exclusive rights, with the right to grant sublicenses, under certain aspects of our intellectual property, to research, develop, make, sell and import drug products and associated diagnostics directed to a specified number of targets identified and/or validated under the agreement. OSI has sole responsibility and is required to use commercially reasonable efforts to develop and commercialize drugs and associated diagnostics directed to the targets to which it has obtained rights.

In November 2010, OSI exercised its option, granted in connection with the July 2009 expansion of our strategic partnership, to obtain:

a non-exclusive license to access our proprietary bioinformatics platform;

non-exclusive perpetual licenses to use bioinformatics data and to use a proprietary gene index related to a specific target pathway; and

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non-exclusive perpetual rights to certain elements of our Human Response Platform and our bioinformatics platform, including the right to obtain certain of our tumor models and tumor archives.

The technology transfer related to the granting of these rights to OSI is expected to be completed in July 2011.

During the remainder of the research program, which will expire in June 2011, neither we nor our affiliates has the right to conduct validation or biomarker research with respect to certain pre-agreed targets that are being, or may be, pursued under our strategic partnership, or to grant any such rights to any third party. Further, during the remainder of the research program, we cannot grant any third party rights to intellectual property used in creating the tumor models and archives to which we granted OSI an option, except that we may grant rights in this intellectual property and these archives to our affiliates and to third parties in connection with the partnering of our existing drug discovery and development programs. We also retain the right to use this intellectual property and these archives for our internal research purposes, including internal use for the benefit of our existing and future third party strategic partners.

Upon entering into the initial collaboration and license agreement with OSI in September 2007, we received a one-time cash payment of \$7.5 million and an equity investment in the amount of \$5.5 million. In July 2009, in connection with the expanded rights we granted to OSI, we received a one-time cash payment of \$5.0 million and an equity investment in the amount of \$15.0 million. On December 1, 2010, we announced that OSI had exercised its option under the parties July 2009 expansion of the agreement to obtain a non-exclusive, perpetual license to certain elements of our propriety technology platform and that OSI will pay us \$25 million in license expansion fees. We received \$12.5 million upon delivery of the notice of option exercise, with the remaining \$12.5 million to be paid following the successful transfer of the applicable technology from us to OSI, which is expected to be completed in July 2011. As of December 31, 2010, we have received approximately \$13.7 million in research and development funding under the agreement, and we will continue to receive research funding to support all individuals we devote to the strategic partnership until expiration of the research program. To date, we have received milestone payments under the agreement in the amount of \$15.3 million, which includes the payment of \$12.5 million in connection with the exercise by OSI of its option to obtain a non-exclusive license to certain elements of our technology platform. If all applicable milestones are achieved, payments for the successful achievement of discovery, development and commercialization milestones under the agreement could total, in the aggregate, over \$94.0 million for each target and its associated products. In addition, OSI is required to make payments to us upon our completion of additional deliverables under the research plan. Upon commercialization of products under the agreement, we are eligible to receive tiered royalty payments on sales of products by OSI, its affiliates and sublicensees. OSI's royalty obligations to us in a particular country begin on the date of first commercial sale of the product in that country, and end on the latest to occur of: (i) 10 years after the first commercial sale of the product, (ii) expiration of regulatory exclusivity applicable to the product (if any) and (iii) the date of expiration of the last to expire issued patent covering the product in the applicable country.

At the conclusion of the research program, we will retain rights to any targets that were included in the strategic partnership but were not selected by OSI. We have also obtained exclusive rights to certain intellectual property developed by OSI under our strategic partnership to develop and commercialize small molecule products and associated diagnostics with respect to the targets that were returned to us, and to develop and commercialize antibody products against any target, other than the targets OSI selected for the development of antibody products. In connection with the licenses granted to us from OSI, we are required to make a one-time milestone payment upon regulatory approval and to pay a royalty on sales of each product where the regulatory approval of the product includes a claim in the product label for a targeted patient population and such claim in the product label is covered by patent rights developed under our strategic partnership.

The collaboration and license agreement will remain in effect until the expiration of both OSI's royalty obligations to us, and our royalty obligations to OSI, in each case determined on a product-by-product and country-by-country basis. OSI has the right to terminate the agreement with respect to any or all collaboration

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targets and all associated products. Either party has the right to terminate the agreement in connection with a material breach of the agreement by the other party that remains uncured for a specified cure period. If OSI elects to terminate the agreement due to our material breach, we will lose our rights to certain intellectual property developed under the strategic partnership, and OSI will have the right to reduce its milestone and royalty obligations to us by the amount of monetary damages suffered by OSI as a direct result of our material breach. If OSI elects to terminate the agreement with respect to one or more collaboration targets and all associated products, OSI's licenses to such targets and products will terminate and revert to us, or if we elect to terminate the agreement due to OSI's material breach of the agreement, OSI's licenses to all targets and products will terminate and revert to us, in either case subject to our continued milestone and royalty payment obligations to OSI, which we will have the right to reduce by the amount of monetary damages we suffer as a direct result of OSI's breach. In addition, if OSI elects to terminate the agreement with respect to one or more collaboration targets and associated products, for a specified time period after such termination OSI and its affiliates may not, nor may they grant third parties the right to, conduct research or development activities with respect to the terminated collaboration target(s).

Biogen Idec

In March 2009, we entered into an exclusive option and license agreement with Biogen Idec International GmbH, a subsidiary of Biogen Idec Inc., which are collectively referred to herein as Biogen Idec, regarding the development and commercialization of our discovery-stage ErbB3-targeted antibodies for the potential treatment and diagnosis of cancer and other diseases outside of the United States, Canada and Mexico. Under the agreement, we are responsible for developing ErbB3 antibodies through completion of the first phase 2 clinical trial designed in a manner that, if successful, will generate data sufficient to support advancement to a phase 3 clinical trial. Within a specified time period after we complete the phase 2 clinical trial and deliver to Biogen Idec a detailed data package containing the results of the trial, Biogen Idec may elect to obtain (1) a co-exclusive (with us), worldwide license, including the right to grant sublicenses, under our relevant intellectual property to develop and manufacture ErbB3 antibody products, and (2) an exclusive license, including the right to grant sublicenses, under our relevant intellectual property, to commercialize ErbB3 antibody products in all countries in the world other than the United States, Canada and Mexico. We retain the exclusive right to commercialize ErbB3 antibody products in the United States, Canada and Mexico. In this description, the countries in the world other than the United States, Canada and Mexico are referred to as Biogen Idec's territory, and the United States, Canada and Mexico are referred to as our territory. If Biogen Idec exercises its exclusive option to ErbB3 antibody products, Biogen Idec will grant us (a) co-exclusive (with Biogen Idec), worldwide license under Biogen Idec's relevant intellectual property, to develop and manufacture ErbB3 antibody products anywhere in the world, and (b) an exclusive license under Biogen Idec's relevant intellectual property, to commercialize ErbB3 antibody products in the United States, Canada and Mexico.

Until completion of the first phase 2 clinical trial, we are solely responsible for the research, development and manufacture of ErbB3 antibody(ies) pursuant to a written work plan meeting specific pre-agreed guidelines. We will share the written work plan with Biogen Idec for its review and comment, and we are required to use commercially reasonable efforts to perform the activities set forth in the work plan. We are solely responsible for all expenses incurred through completion of the first phase 2 clinical trial. If Biogen Idec exercises its option to obtain exclusive commercialization rights to ErbB3 products in its territory, we will then be solely responsible, subject to a mutually agreed development plan, budget and the oversight of a joint development committee, for the global development of ErbB3 antibody products, except that Biogen Idec will be solely responsible for ErbB3 antibody product development activities that relate solely to the Biogen Idec territory. Further, neither party has the right to conduct development activities in its respective territory if those development activities would materially and adversely affect the development of ErbB3 antibody products in the other party's territory. We and Biogen Idec will share global development costs (including manufacturing costs to support development) for ErbB3 antibody products equally, except that Biogen Idec will be solely responsible for all development costs associated solely with the development of ErbB3 antibody products for its territory, and we will be solely responsible for all development costs associated solely with the development of ErbB3 antibody products for the

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United States, Canada and Mexico. If either party wishes to develop a new ErbB3 antibody product under the agreement, and the other party does not also wish to develop that product, the party that desires to conduct development activities regarding the new ErbB3 antibody product has the right to independently, and at its sole cost, develop and manufacture the new ErbB3 antibody product for commercialization solely in its territory.

We are solely responsible for, and obligated to use commercially reasonable efforts to, manufacture and supply clinical and commercial quantities of ErbB3 antibody products for the Biogen Idec territory and for the United States, Canada and Mexico. If we determine to retain a third party to manufacture and supply ErbB3 antibody products for phase 3 clinical trials and/or for commercialization in the United States, Canada and Mexico or the Biogen Idec territory, then we must first notify Biogen Idec thereof, and, subject to certain limitations, Biogen Idec may elect to become the sole supplier of ErbB3 antibody product for phase 3 clinical trials and for worldwide commercialization.

Pursuant to the agreement, commercialization efforts will be discussed and coordinated at meetings of the joint commercialization committee, comprised of our and Biogen Idec's representatives. We have the sole right, at our sole expense (including manufacturing costs), to commercialize ErbB3 antibody products in the United States, Canada and Mexico, and we are required to use commercially reasonable efforts to do so in countries in our territory where marketing approval has been obtained. Biogen Idec has the sole right, at its sole expense (including manufacturing costs) to commercialize ErbB3 antibody products in its territory, and is required to use commercially reasonable efforts to do so in countries in its territory where marketing approval has been obtained.

We have agreed that, prior to Biogen Idec's exercise of its exclusive option, or until the expiration of Biogen Idec's option right, we and our affiliates will not grant any third party rights to develop ErbB3 antibodies in our territory or in the Biogen Idec territory. We have also agreed that, during the term of the agreement, we will not grant any third party rights to develop or commercialize ErbB3 antibody products if such third party is independently developing or commercializing its own product containing an ErbB3 antibody. Prior to entering into discussions with, or granting a license or sublicense to, any third party with respect to the commercialization of ErbB3 antibody products, we are required to negotiate in good faith with Biogen Idec for a limited time period with respect to granting such rights to Biogen Idec. We have also agreed that, except pursuant to our agreement with Biogen Idec, during the term of the agreement, neither we nor our affiliates, alone or with or on behalf of any third party, will develop, manufacture or commercialize any ErbB3 antibody for therapeutic or diagnostic use in humans, or grant rights to any third party to do any of the foregoing.

Upon entering into the exclusive option and license agreement with Biogen Idec, we received a one-time cash payment in the amount of \$5.0 million and an equity investment in the amount of \$30.0 million. In each of June 2009 and April 2010, we received a \$5.0 million milestone payment for achievement of the first two pre-clinical discovery milestones under the agreement. We could also receive (i) additional pre-clinical discovery and development milestone payments of \$5.0 million in the aggregate, and (ii) if Biogen Idec exercises its option to obtain exclusive rights to commercialize ErbB3 antibody products in its territory, an option exercise fee and regulatory milestone payments of \$50.0 million in the aggregate. If Biogen Idec exercises its exclusive option, Biogen Idec will pay us royalties on its sales of ErbB3 antibody products in the Biogen Idec territory, and we will pay Biogen Idec royalties on our sales of ErbB3 antibody products in the United States, Canada and Mexico. Biogen Idec's royalty obligations to us, and our royalty obligations to Biogen Idec, determined on a product-by-product and country-by-country basis, commence on the first commercial sale of the ErbB3 antibody product in the applicable country, and expire on the later of the date of expiration of (1) the last applicable patent covering the ErbB3 antibody product in the applicable country, and (2) any regulatory exclusivity applicable to the ErbB3 antibody product in that country.

If Biogen Idec fails to exercise its exclusive option to co-develop and commercialize ErbB3 antibody products, then the agreement will terminate on the date Biogen Idec's option right expires, and we will retain all of our rights to develop, manufacture and commercialize our ErbB3 antibody products. If Biogen Idec exercises its exclusive option to co-develop and commercialize ErbB3 antibody products, then, unless earlier terminated,

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the agreement will remain in effect until the last to expire of all royalty obligations under the agreement, or, if later, upon completion of any development activities that were pending before the expiration of all royalty obligations under the agreement.

Biogen Idec may terminate the agreement for convenience with respect to any product(s), by providing us with three months' prior written notice. Either party may terminate the agreement due to a material breach of the agreement by the other party that is not cured within a short period.

If Biogen Idec terminates the agreement for convenience, or if we terminate the agreement due to a material breach of the agreement by Biogen Idec, in each case prior to Biogen Idec's exercise of its exclusive option (and prior to the expiration of the option exercise period), then Biogen Idec's exclusive option will terminate.

If Biogen Idec terminates the agreement for convenience, or if we terminate the agreement due to a material breach of the agreement by Biogen Idec, in each case with respect to one or more ErbB3 antibody products after Biogen Idec's exercise of its exclusive option, then at our election, (1) Biogen Idec will lose all rights to the terminated product(s), (2) we will have the worldwide right to develop, manufacture and commercialize the terminated product(s), subject to milestone and royalty obligations to Biogen Idec in our territory and in the Biogen Idec territory, and (3) Biogen Idec will be required to transfer to us all regulatory approvals, data, promotional materials and other documents, materials and information reasonably necessary to enable us to develop, manufacture and commercialize the terminated products in the Biogen Idec territory. Further, in the case of termination by Biogen Idec for convenience, Biogen Idec will be required to continue to pay its share of all development costs with respect to the terminated product for a specified period after the effective date of termination.

If Biogen Idec terminates the agreement due to our material breach of the agreement, at Biogen Idec's election (1) if not yet exercised, Biogen Idec will be deemed to have exercised its exclusive option and will not be required to pay us the option exercise fee, (2) Biogen Idec will have no further milestone payment obligations to us, (3) we will lose all rights to the terminated product(s), (4) Biogen Idec will have the worldwide right to develop, manufacture and commercialize the terminated product(s), subject to royalty obligations to us based on worldwide net sales, and (5) we will be required to transfer to Biogen Idec all regulatory approvals, data, promotional materials and other documents, materials and information reasonably necessary to enable Biogen Idec to develop, manufacture and commercialize the terminated products in the Biogen Idec's territory.

If all of our assets are acquired by, or we merge with, another entity, and the other entity is independently developing or commercializing a product containing an ErbB3 antibody and fails to divest the ErbB3 product within a specified time period, Biogen Idec will have the option to either terminate the agreement or maintain the agreement. If Biogen Idec elects to terminate the agreement, then each party will have the right to develop, manufacture and commercialize ErbB3 antibody products for its respective territory, subject to reduced royalty obligations to the other party, and Biogen Idec's activities will not be subject to the oversight of the joint committee. If Biogen Idec elects to maintain the agreement, Biogen Idec will have the right to assume the key development, manufacturing, budgeting and governance rights, responsibilities, and obligations under the agreement that had previously been our rights and obligations.

Merck

Target Identification Collaboration

In November 2003, we entered into a license and collaboration agreement with Merck to discover and validate oncology targets. During the research program portion of the collaboration, which concluded in November 2006, we used our proprietary cancer models to identify and subsequently validate essential tumor maintenance genes suitable as targets for small molecule drug development. During the research program, Merck exercised its option with respect to, and we granted Merck an exclusive, worldwide license, with the right to grant sublicenses, to six molecular targets, and associated data, discovered and validated by us under the research

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collaboration, to develop, manufacture and commercialize small molecule products directed to such targets for therapeutic use. In conjunction with the exclusive license granted to Merck, we granted Merck non-exclusive licenses, with the right to grant sublicenses, to (1) develop, manufacture and commercialize products and compounds directed at certain targets for diagnostic use, and (2) develop, manufacture and use biological products (antibodies, proteins, polypeptides, etc.) directed at certain targets solely for the research or development of products for therapeutic and/or diagnostic use. We also granted Merck a non-exclusive right to use data generated during the collaboration, not related to the six collaboration targets exclusively licensed by Merck, solely for Merck's and its affiliates' internal research purposes. Except for the six collaboration targets selected by Merck, we retain all of our rights to targets that were explored under the research collaboration. Merck is solely responsible for drug discovery, clinical development and commercialization of the products directed to the six collaboration targets it selected.

Upon entering into the agreement with Merck, we received a \$7.0 million cash up-front payment. Over the course of the three-year research program, we received approximately \$6.0 million in research funding, and as of December 31, 2010, we have received milestone payments of approximately \$300,000. The collaboration was expanded in April 2005, and as part of that expansion, we received a \$5.0 million equity investment. We also received cash payments of \$2.0 million in each of May 2005 and April 2006 in return for providing Merck with rights to advance a pre-agreed number of targets into high-throughput screening. In addition, if all development and regulatory milestones are reached with respect to each of the six targets, potential additional milestone payments could total, in the aggregate, \$249.0 million. We are also eligible to receive tiered royalties from Merck based on the sales of products that are directed to or use the collaboration targets selected by Merck. Merck's royalty obligations in a particular country begin on the date of first commercial sale of a product in that country, and end on the later of 10 years after the date of first commercial sale of the product in that country or the date of the last to expire of the issued patents covering the product in that country.

Our agreement with Merck will remain in effect for the length of Merck's royalty obligation to us, determined on a product-by-product and country-by-country basis. Merck has the right to terminate the agreement at any time, in its sole discretion, upon 120 days' prior written notice to us. Either party has the right to terminate the agreement in connection with a material breach of the agreement by the other party that remains uncured for a specified cure period. If Merck terminates the agreement at will, or if we terminate the agreement due to Merck's material breach of the agreement, Merck's licenses to develop, manufacture, and commercialize products directed to or using the collaboration targets will terminate, and we will be permitted to use the data generated under our collaboration to research, develop and commercialize products directed to such targets.

Biomarker Identification Collaboration

In August 2005, we entered into our second collaboration with Merck, a license and research collaboration agreement relating to the use of our Human Response Platform. The collaboration concluded in December 2007 and was focused on the identification of genetic profiles that correlate with drug response to certain cancer compounds then under development at Merck, in order to more effectively guide Merck's clinical and market development of these compounds.

Under the terms of the agreement, Merck obtained exclusive rights to all inventions and discoveries developed in the conduct of the collaborative research program that relate to Merck's proprietary cancer compounds, including gene expression patterns that correlate with a response to Merck's compounds. We and Merck jointly own the rights to all inventions and discoveries developed in the conduct of the collaborative research program that relate to control compounds (i.e. non-Merck compounds), including gene expression patterns that correlate with a response to the control compounds. Upon entering into the license and research collaboration agreement with Merck, we received a \$2.0 million equity investment, and over the course of the collaborative research program we received approximately \$4.5 million in research funding. If all development and regulatory milestones under the agreement are achieved, potential milestone payments could total, in the aggregate, \$4.9 million.

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Either party may terminate the agreement in the event of an uncured material breach by, or a bankruptcy event of, the other party. If Merck terminates the agreement due to our material breach of the agreement, Merck's payment obligations to us will also terminate. Merck may terminate the agreement at any time for convenience by providing us with at least 120 days' prior written notice, however, Merck's payment obligations to us will continue after such termination if the applicable milestone events are achieved. If the license and research collaboration agreement is not terminated as described above, the agreement will continue in effect until the expiration of all of Merck's payment obligations to us under the agreement.

Patents and Proprietary Rights

General Intellectual Property Considerations

We have been building and will seek to continue to build a strong intellectual property portfolio. In this regard, we have focused on patents, patent applications and other intellectual property covering:

tivozanib and related technologies

U.S. patents: 5 issued; 1 pending; expirations ranging from 2018 to 2030

European patents: 3 granted; none pending; expirations ranging from 2018 to 2023

Canadian patents: none granted; 1 pending; expiration 2022

Australian patents: 1 granted; none pending; expiration 2022

International applications: 3 pending; expirations ranging from 2029 to 2030

our antibody product pipeline and related technologies

U.S. patents: 3 issued; 8 pending; expirations ranging from 2027 to 2031

European patents: 1 granted; 4 pending; expirations 2027 to 2029

International applications: none pending

various facets of our technology platform

U.S. patents: 4 issued; 2 pending; expirations ranging from 2020 to 2025

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European patents: 1 granted; 3 pending; expirations ranging from 2022 to 2026

Australian patents: 2 granted; 2 pending; expirations ranging from 2022 to 2026

We strive for multi-tiered patent protection, where possible. For example, with respect to tivozanib, we have exclusively licensed patents that cover the molecule and its therapeutic use (patent expiration 2022, with the possibility of patent term extension to 2025 in the United States), a key step in manufacturing the molecule, and a crystal form of the molecule, i.e., a polymorph with low hygroscopicity used in the clinical formulation. Complementing these in-licensed patents relating to tivozanib are two of our own issued U.S. patents that cover different biomarker tests for identifying human patients likely to respond to treatment with tivozanib, and a pending application on a method of using tivozanib in combination with temsirolimus.

We own issued U.S. patents containing composition-of-matter claims that cover our HGF antibodies, including ficlatuzumab. In addition, we own pending patent applications covering our HGF antibodies, our FGFR3 antibodies, ErbB3 antibodies, FGFR2 antibodies, EGFR antibodies, RON antibodies, Notch1 antibodies, and methods of making and using those antibodies. We are prepared to file patent applications on the other antibodies in our antibody product pipeline soon after the experimental data necessary for an application becomes available.

In addition to filing and prosecuting patent applications in the United States, we file counterpart patent applications in Europe, Canada, Japan, Australia (and sometimes additional countries), in cases where we think such foreign filing is likely to be cost-effective.

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The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the earliest date of filing a non-provisional patent application. In the United States, a patent's term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the U.S. Patent and Trademark Office in granting a patent, or may be shortened if a patent is terminally disclaimed over another patent.

The patent term of a patent that covers an FDA-approved drug may also be eligible for patent term extension, which permits patent term restoration as compensation for the patent term lost during the FDA regulatory review process. The Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act, permits a patent term extension of up to five years beyond the expiration of the patent. The length of the patent term extension is related to the length of time the drug is under regulatory review. Patent extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval and only one patent applicable to an approved drug may be extended. Similar provisions are available in Europe and other foreign jurisdictions to extend the term of a patent that covers an approved drug. In the future, if and when our pharmaceutical products receive FDA approval, we expect to apply for patent term extensions on patents covering those products.

In addition, our patent portfolio contains a number of patents and patent applications relevant to our business. For example, we own a granted U.S. patent and pending foreign counterpart applications covering a method of making a chimeric mouse cancer model. We also own a granted U.S. patent and pending foreign counterpart patent applications covering a method of producing primary tumor material via directed complementation. We also own pending U.S. and foreign patent applications covering a mouse model that contains a human breast tumor. Furthermore, we own a granted U.S. patent and a pending foreign counterpart patent application covering a method of identifying cancer tissue likely to be sensitive or resistant to treatment with an inhibitor of Notch receptor activation. Besides having a portfolio of patents and pending patent applications owned by us covering our platform technology, we are exclusively licensed under Dana-Farber patents that cover germ line transgenic mouse models of cancer, and a method of using spontaneous inducible mouse tumor models to screen for, and identify, novel targets for new cancer drugs, which we refer to as our MaSS screen technology.

For some aspects of our proprietary technology, trade secret protection is more appropriate than patent protection. For example, our proprietary bioinformatics software tools and databases are protected as trade secrets. Our bioinformatics tools and databases give us the means to store, analyze, interpret and integrate the large volume of data generated from our various tumor models and from analysis of human clinical samples from clinical trials. We continually make incremental improvements in our proprietary software tools, as we tailor them to the changing needs of our research and development programs. In general, trade secret protection can accommodate this continuing evolution of our bioinformatics system better than other forms of intellectual property protection.

Many pharmaceutical companies, biotechnology companies and academic institutions are competing with us in the field of oncology and filing patent applications potentially relevant to our business. In order to contend with the inevitable possibility of third party intellectual property conflicts, we make freedom-to-operate studies an ongoing part of our business operations. With regard to tivozanib, we are aware of a third party United States patent, and corresponding foreign counterparts, that contain broad claims related to the use of an organic compound that, among other things, inhibits tyrosine phosphorylation of a VEGF receptor caused by VEGF binding to such VEGF receptor. We are also aware of third party United States patents that contain broad claims related to the use of a tyrosine kinase inhibitor in combination with a DNA damaging agent such as chemotherapy or radiation and we have received written notice from the owners of such patents indicating that they believe we may need a license from them in order to avoid infringing their patents. With regard to ficlatuzumab, we are aware of two separate families of United States patents, United States patent applications and foreign counterparts, with each of the two families being owned by a different third party, that contain broad claims related to anti-HGF antibodies having certain binding properties and their use. We are aware of a

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United States patent that contains claims related to a method of treating a tumor by administering an agent that blocks the ability of HGF to promote angiogenesis in the tumor. With regard to AV-203, we are aware of a third party United States patent that contains broad claims relating to anti-ErbB3 antibodies. Based on our analyses, if any of the above third party patents were asserted against us, we do not believe our proposed products or activities would be found to infringe any valid claim of these patents. If we were to challenge the validity of any issued United States patent in court, we would need to overcome a statutory presumption of validity that attaches to every United States patent. This means that in order to prevail, we would have to present clear and convincing evidence as to the invalidity of the patent's claims. There is no assurance that a court would find in our favor on questions of infringement or validity.

From time to time, we find it necessary or prudent to obtain licenses from third party intellectual property holders. Where licenses are readily available at reasonable cost, such licenses are considered a normal cost of doing business. In other instances, however, we may use the results of freedom-to-operate studies to guide our early-stage research away from areas where we are likely to encounter obstacles in the form of third party intellectual property. For example, where a third party holds relevant intellectual property and is a direct competitor, a license might not be available on commercially reasonable terms or available at all. We strive to identify potential third party intellectual property issues in the early stages of research of our research programs, in order to minimize the cost and disruption of resolving such issues.

In spite of these efforts to avoid obstacles and disruptions arising from third party intellectual property, it is impossible to establish with certainty that our technology platform or our product programs will be free of claims by third party intellectual property holders. Even with modern databases and on-line search engines, literature searches are imperfect and may fail to identify relevant patents and published applications. Even when a third party patent is identified, we may conclude upon a thorough analysis, that we do not infringe the patent or that the patent is invalid. If the third party patent owner disagrees with our conclusion and we continue with the business activity in question, we might have patent litigation initiated against us. Alternatively, we might decide to initiate litigation in an attempt to have a court declare the third party patent invalid or non-infringed by our activity. In either scenario, patent litigation typically is costly and time-consuming, and the outcome is uncertain. The outcome of patent litigation is subject to uncertainties that cannot be quantified in advance, for example, the credibility of expert witnesses who may disagree on technical interpretation of scientific data. Ultimately, in the case of an adverse outcome in litigation, we could be prevented from commercializing a product or using certain aspects of our technology platform as a result of patent infringement claims asserted against us. This could have a material adverse affect on our business.

To protect our competitive position, it may be necessary to enforce our patent rights through litigation against infringing third parties. Litigation to enforce our own patent rights is subject to the same uncertainties discussed above. In addition, however, litigation involving our patents carries the risk that one or more of our patents will be held invalid (in whole or in part, on a claim-by-claim basis) or held unenforceable. Such an adverse court ruling could allow third parties to commercialize our products or our platform technology, and then compete directly with us, without payment to us.

In-Licenses

Dana-Farber Cancer Institute. When forming the company in March 2002, we entered into a license agreement with Dana-Farber Cancer Institute, or DFCI. Under the agreement, we have: exclusive, worldwide rights under certain DFCI patents and patent applications relating to spontaneous, inducible mouse tumor models; the right to grant sublicenses; and sole ownership rights to any improvements made solely by our employees to the mouse model technology licensed from DFCI. We have fulfilled certain milestone payment obligations to DFCI. We will have no royalty obligation to DFCI based on sales of products discovered, designed, developed or tested using the licensed mouse tumor models. Our license from DFCI will expire on the expiration date of the last-to-expire of the underlying patents.

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Kyowa Hakko Kirin. In December 2006, we entered into a license agreement with Kirin Brewery Co. Ltd. (now Kyowa Hakko Kirin) under which we obtained an exclusive license to research, develop, manufacture and commercialize tivozanib (f/k/a KRN951), pharmaceutical compositions thereof and associated biomarkers for the diagnosis, prevention and treatment of any and all human diseases and conditions. Our exclusive license covers all territories in the world, except for Asia. Kyowa Hakko Kirin has retained rights to tivozanib in Asia. For further discussion of this agreement, please see Strategic Partnerships Kyowa Hakko Kirin.

Other. We hold several non-exclusive licenses from other third parties that give us access to various technologies involved in building and using our technology platform and discovering and developing our antibody pipeline.

Manufacturing

We currently contract with third parties for the manufacture of our product candidates for preclinical studies and clinical trials and intend to do so in the future. We do not own or operate manufacturing facilities for the production of clinical or commercial quantities of our product candidates. We currently have no plans to build our own clinical or commercial scale manufacturing capabilities. To meet our projected needs for commercial manufacturing, third parties with whom we currently work will need to increase their scale of production or we will need to secure alternate suppliers. Although we rely on contract manufacturers, we have personnel with extensive manufacturing experience to oversee the relationships with our contract manufacturers.

One of our contract manufacturers has manufactured what we believe to be sufficient quantities of tivozanib's drug substance to support the ongoing phase 1, 2 and 3 clinical trials. We believe the current manufacturing process for the drug substance for tivozanib is adequate to support future development and commercial demand. In addition, we currently engage a separate contract manufacturer to manufacture, package and distribute clinical supplies of tivozanib. While we believe that our existing suppliers of drug substance and drug product would be capable of producing commercial quantities, we will need to fully validate their ability to produce drug substance and drug product on commercial scale and establish contractual relationships with them to secure supply on a commercial basis. If we are unable to validate our third-party manufacturing sources' ability to supply on a commercial basis, or fail to establish commercially reasonable terms for commercial supply, we may not be able to successfully produce and market tivozanib.

As of December 27, 2010, the effective date of the termination of our collaboration with Merck relating to ficlatuzumab, we became responsible for all process development and all manufacturing of ficlatuzumab for future development and commercialization. Prior to Merck's termination of its collaboration agreement with us, multiple batches of drug product were produced by Merck to support clinical trials of ficlatuzumab through phase 2 clinical trials. Pursuant to the terms of our agreement with Merck, we are currently in discussions with Merck regarding the purchase of amounts of clinical supply of ficlatuzumab which supply we expect will allow us to complete our ongoing phase 1 and phase 2 clinical trials of ficlatuzumab. While we believe that the existing batches we expect will be purchased from Merck are adequate to support the ongoing clinical trials, we will need to identify a third party manufacturer capable of producing quantities of drug substance and drug product to support other clinical trials, including planned phase 3 clinical trials and commercial quantities. If we are unable to arrange for purchase of sufficient amounts of clinical supply of ficlatuzumab from Merck or identify a third-party manufacturing source, or fail to do so on commercially reasonable terms, we may not be able to successfully further develop and market ficlatuzumab.

To date, our third-party manufacturers have met our manufacturing requirements. We believe that there are alternate sources of supply that can satisfy our clinical and commercial requirements, although we cannot be certain that identifying and establishing relationships with such sources, if necessary, would not result in significant delay or material additional costs.

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Sales and Marketing

If tivozanib is approved for sale, it is our goal to maximize its potential value in the U.S. and Europe by demonstrating tivozanib's potential favorable efficacy and safety profile and establishing tivozanib as a first-line treatment of choice for patients with advanced RCC.

In order to achieve this goal, we recently entered into a strategic partnership with Astellas in connection with which we and Astellas will develop and commercialize tivozanib in North America and Europe. We intend to build a commercial infrastructure in the United States necessary to effectively support the commercialization of tivozanib and future oncology products, if approved. The commercial infrastructure for specialty oncology products typically consists of a targeted, field based specialty sales force that calls on a focused group of physicians. This sales force would be supported by sales management, as well as internal and outsourced commercial groups including sales operations, marketing, market research, reimbursement services and distribution. Additional capabilities important to the oncology marketplace include the management of key accounts such as managed care organizations, group-purchasing organizations, specialty pharmacies, oncology group networks, and government accounts, all responsibilities and costs which we will share with our partner, Astellas. To develop the appropriate commercial infrastructure, we will have to invest significant amounts of financial and management resources, some of which will be committed prior to any confirmation that tivozanib will be approved. In Europe, although Astellas will be the lead commercialization party, we are obligated to contribute up to 50% of the medical science liaisons in the major European countries as well as formulate with Astellas the European commercial strategy, including the strategic plan and allocation of resources.

Government Regulation

Government authorities in the United States (including federal, state and local authorities) and in other countries, extensively regulate, among other things, the manufacturing, research and clinical development, marketing, labeling and packaging, distribution, post-approval monitoring and reporting, advertising and promotion, and export and import of pharmaceutical products, such as those we are developing. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources.

United States Government Regulation

In the United States, the U.S. Food and Drug Administration, or FDA, regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and related regulations. Drugs are also subject to other federal, state and local statutes and regulations. Biological products are subject to regulation by the FDA under the FDCA, the Public Health Service Act, and related regulations, and other federal, state and local statutes and regulations. Failure to comply with the applicable U.S. regulatory requirements at any time during the product development process, approval process or after approval, may subject an applicant to administrative or judicial sanctions. These sanctions could include the imposition by the FDA or an Institutional Review Board, or IRB, of a clinical hold on trials, the FDA's refusal to approve pending applications or supplements, withdrawal of an approval, warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties or criminal prosecution. Any agency or judicial enforcement action could have a material adverse effect on us.

The Investigational New Drug Process

An Investigational New Drug application, or an IND, is a request for authorization from the FDA to administer an investigational drug or biological product to humans. Such authorization must be secured prior to interstate shipment (usually to clinical investigators) and administration of any new drug or biological product to humans that is not the subject of an approved New Drug Application or Biologics License Application, except under limited circumstances.

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To conduct a clinical investigation with an investigational new drug or biological product, we are required to file an IND with the FDA in compliance with Title 21 of the Code of Federal Regulations (CFR), Part 312. These regulations contain the general principles underlying the IND submission and the general requirements for an IND's content and format.

The central focus of the initial IND submission is on the general investigational plan and the protocol(s) for human studies. The IND also includes results of animal studies or other human studies, as appropriate, as well as manufacturing information, analytical data and any available clinical data or literature to support the use of the investigational new drug or biological product. An IND must become effective before human clinical trials may begin. An IND will automatically become effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to the proposed clinical trials as outlined in the IND. In such a case, the IND may be placed on clinical hold and the IND sponsor and the FDA must resolve any outstanding concerns or questions before clinical trials can begin. Accordingly, submission of an IND may or may not result in the FDA allowing clinical trials to commence.

Clinical trials involve the administration of the investigational drug or biological product to patients under the supervision of qualified investigators in accordance with Good Clinical Practices, or GCPs. Clinical trials are conducted under protocols detailing, among other things, the objectives of the study, the parameters to be used in monitoring safety, and the efficacy criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. Additionally, approval must also be obtained from each clinical site's independent IRB before the trials may be initiated. All participants in our clinical trials must provide their informed consent in writing in compliance with GCPs and the ethical principles that have their origin in the Declaration of Helsinki.

The clinical investigation of an investigational drug or biological product is generally divided into three phases. Although the phases are usually conducted sequentially, they may overlap or be combined. The three phases of an investigation are as follows:

Phase 1. Phase 1 includes the initial introduction of an investigational new drug or biological product into humans. Phase 1 clinical trials are typically closely monitored and may be conducted in patients with the target disease or condition or healthy volunteers. These studies are designed to evaluate the safety, dosage tolerance, metabolism and pharmacologic actions of the investigational drug or biological product in humans, the side effects associated with increasing doses, and if possible, to gain early evidence on effectiveness. During phase 1 clinical trials, sufficient information about the investigational drug's or biological product's pharmacokinetics and pharmacological effects may be obtained to permit the design of well-controlled and scientifically valid phase 2 clinical trials. The total number of participants included in phase 1 clinical trials varies, but is generally in the range of 20 to 80.

Phase 2. Phase 2 includes the controlled clinical trials conducted to preliminarily or further evaluate the effectiveness of the investigational drug or biological product for a particular indication(s) in patients with the disease or condition under study, to determine dosage tolerance and optimal dosage, and to identify possible adverse side effects and safety risks associated with the drug or biological product. Phase 2 clinical trials are typically well-controlled, closely monitored, and conducted in a limited patient population, usually involving no more than several hundred participants.

Phase 3. Phase 3 clinical trials are generally controlled clinical trials conducted in an expanded patient population generally at geographically dispersed clinical trial sites. They are performed after preliminary evidence suggesting effectiveness of the drug or biological product has been obtained, and are intended to further evaluate dosage, clinical effectiveness and safety, to establish the overall benefit-risk relationship of the investigational drug or biological product, and to provide an adequate basis for product approval. Phase 3 clinical trials usually involve several hundred to several thousand participants.

The FDA's primary objectives in reviewing an IND are to assure the safety and rights of patients and to help assure that the quality of the investigation will be adequate to permit an evaluation of the drug's effectiveness.

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and safety and of the biological product's safety, purity and potency. The decision to terminate development of an investigational drug or biological product may be made by either a health authority body such as the FDA (or IRB/ethics committees), or by us for various reasons. Additionally, some trials are overseen by an independent group of qualified experts organized by the trial sponsor, known as a data safety monitoring board or committee. This group provides authorization for whether or not a trial may move forward at designated check points based on access that only the group maintains to available data from the study. Suspension or termination of development during any phase of clinical trials can occur if it is determined that the participants or patients are being exposed to an unacceptable health risk. Other reasons for suspension or termination may be made by us based on evolving business objectives and/or competitive climate.

In addition, there are requirements and industry guidelines to require the posting of ongoing clinical trials on public registries, and the disclosure of designated clinical trial results.

Assuming successful completion of all required testing in accordance with all applicable regulatory requirements, detailed investigational drug or biological product information is submitted to the FDA in the form of an NDA or Biologics License Application, or BLA, requesting approval to market the product for one or more indications.

The NDA/BLA Approval Process

In order to obtain approval to market a drug or biological product in the United States, a marketing application must be submitted to the FDA that provides data establishing the safety and effectiveness of the drug product for the proposed indication, and the safety, purity and potency of the biological product for its intended indication. The application includes all relevant data available from pertinent preclinical and clinical trials, including negative or ambiguous results as well as positive findings, together with detailed information relating to the product's chemistry, manufacturing, controls and proposed labeling, among other things. Data can come from company-sponsored clinical trials intended to test the safety and effectiveness of a use of a product, or from a number of alternative sources, including studies initiated by investigators. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety and effectiveness of the investigational drug product and the safety, purity and potency of the biological product to the satisfaction of the FDA.

The steps required before an investigational drug or biological product may be marketed in the United States generally include:

Completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA's Good Laboratory Practices, or GLP, regulations;

Submission to the FDA of an IND to support human clinical testing;

Approval by an IRB at each clinical site before each trial may be initiated;

Performance of adequate and well-controlled clinical trials in accordance with GCP to establish the safety and efficacy of the investigational drug product for each targeted indication or the safety, purity and potency of the biological product for its intended indication;

Submission of an NDA or BLA to the FDA;

Satisfactory completion of an FDA Advisory Committee review, if applicable;

Satisfactory completion of an FDA inspection of the manufacturing facilities at which the investigational drug or biological product is produced to assess compliance with current good manufacturing practices, or cGMP, and to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality and purity; and

FDA review and approval of the NDA or BLA.

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In most cases, the NDA or BLA must be accompanied by a substantial user fee; there may be some instances in which the user fee is waived.

The FDA will initially review the NDA or BLA for completeness before it accepts the NDA or BLA for filing. The FDA has 60 days from its receipt of an NDA to determine whether the application will be accepted for filing based on the agency's threshold determination that it is sufficiently complete to permit substantive review. After the NDA submission is accepted for filing, the FDA reviews the NDA to determine, among other things, whether the proposed product is safe and effective for its intended use, and whether the product is being manufactured in accordance with cGMP to assure and preserve the product's identity, strength, quality and purity. The FDA reviews a BLA to determine, among other things, whether the product is safe, pure and potent and the facility in which it is manufactured, processed, packaged or held meets standards designed to assure the product's continued safety, purity and potency. The FDA may refer applications for novel drug or biological products or drug or biological products which present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Before approving an NDA or BLA, the FDA will inspect the facilities at which the product is manufactured. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving an NDA or BLA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP. If the FDA determines the application, manufacturing process or manufacturing facilities are not acceptable, it will outline the deficiencies in the submission and often will request additional testing or information. Notwithstanding the submission of any requested additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

The testing and approval process requires substantial time, effort and financial resources, and each may take several years to complete. Data obtained from clinical activities are not always conclusive and may be susceptible to varying interpretations, which could delay, limit or prevent regulatory approval. The FDA may not grant approval on a timely basis, or at all. We may encounter difficulties or unanticipated costs in our efforts to develop our product candidates and secure necessary governmental approvals, which could delay or preclude us from marketing our products. Even if the FDA approves a product, it may limit the approved indications for use or place other conditions on any approvals that could restrict the commercial application of the products such as a requirement that we implement special risk management measures through a Risk Evaluation and Mitigation Strategy. After approval, some types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Post-Approval Regulation

After regulatory approval of a drug or biological product is obtained, we are required to comply with a number of post-approval requirements. For example, as a condition of approval of an NDA or BLA, the FDA may require post-marketing testing, including phase 4 clinical trials, and surveillance to further assess and monitor the product's safety and effectiveness after commercialization. Regulatory approval of oncology products often requires that patients in clinical trials be followed for long periods to determine the overall survival benefit of the drug or biologic. In addition, as a holder of an approved NDA or BLA, we would be required to report, among other things, certain adverse reactions and production problems to the FDA, to provide updated safety and efficacy information, and to comply with requirements concerning advertising and promotional labeling for any of our products. Also, quality control and manufacturing procedures must continue to conform to cGMP after approval to assure and preserve the long term stability of the drug or biological

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product. The FDA periodically inspects manufacturing facilities to assess compliance with cGMP, which imposes extensive procedural, substantive and record keeping requirements. In addition, changes to the manufacturing process are strictly regulated, and, depending on the significance of the change, may require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon us and any third party manufacturers that we may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain compliance with cGMP and other aspects of regulatory compliance.

We rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of our product candidates. Future FDA and state inspections may identify compliance issues at our facilities or at the facilities of our contract manufacturers that may disrupt production or distribution, or require substantial resources to correct. In addition, discovery of previously unknown problems with a product or the failure to comply with applicable requirements may result in restrictions on a product, manufacturer or holder of an approved NDA or BLA, including withdrawal or recall of the product from the market or other voluntary, FDA-initiated or judicial action that could delay or prohibit further marketing. Newly discovered or developed safety or effectiveness data may require changes to a product's approved labeling, including the addition of new warnings and contraindications, and also may require the implementation of other risk management measures. Also, new government requirements, including those resulting from new legislation, may be established, or the FDA's policies may change, which could delay or prevent regulatory approval of our products under development.

Europe / Rest of World Government Regulation

In addition to regulations in the United States, we will be subject to a variety of regulations in other jurisdictions governing, among other things, clinical trials and any commercial sales and distribution of our products.

Whether or not we obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical trial application much like the IND prior to the commencement of human clinical trials. In Europe, for example, a clinical trial application, or CTA, must be submitted to each country's national health authority and an independent ethics committee, much like the FDA and IRB, respectively. Once the CTA is approved in accordance with a country's requirements, and relevant ethics committees have issued positive opinions, the clinical trial covered by the CTA may proceed.

The requirements and process governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, the clinical trials are conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

To obtain regulatory approval of an investigational drug or biological medicinal product under European Union regulatory systems, we must submit a marketing authorization application. The application used to file the NDA or BLA in the United States is similar to that required in Europe, with the exception of, among other things, country-specific document requirements.

For other countries outside of the European Union, such as countries in Eastern Europe, Latin America or Asia, the requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, again, the clinical trials are conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

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If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

Compliance

During all phases of development (pre- and post-marketing), failure to comply with the applicable regulatory requirements may result in administrative or judicial sanctions. These sanctions could include the FDA's imposition of a clinical hold on trials or the suspension of clinical trials by other regulatory authorities, refusal to approve pending applications, withdrawal of an approval, warning letters, product recalls, product seizures, total or partial suspension of production or distribution, product detention or refusal to permit the import or export of products, injunctions, fines, civil penalties or criminal prosecution. Any agency or judicial enforcement action could have a material adverse effect on us.

Available Special Regulatory Procedures

Formal Meetings

We are encouraged to engage and seek guidance from health authorities relating to the development and review of investigational drugs and biologics, as well as marketing applications. In the United States, there are different types of official meetings that may occur between us and the FDA. Each meeting type is subject to different procedures. Conclusions and agreements from each of these meetings are captured in the official final meeting minutes issued by the FDA.

The EMA and national medicines regulators within the EU also provide the opportunity for dialogue with us. At the EMA level, this is usually done in the form of Scientific Advice, which is given by the Scientific Advice Working Party of the Committee for Medicinal Products for Human Use, or CHMP. A fee is incurred with each Scientific Advice procedure.

Advice from either the FDA or EMA is typically provided based on questions concerning, for example, quality (chemistry, manufacturing and controls testing), nonclinical testing and clinical studies, and pharmacovigilance plans and risk-management programs. Advice is not legally binding with regard to any future marketing authorization application of the product concerned. To obtain binding commitments from the FDA, Special Protocol Assessment or Protocol Assistance procedures are available. Where the FDA agrees to a Special Protocol Assessment, or SPA, the agreement may not be changed by either the sponsor or the FDA except if the sponsor and the FDA agree to a change, or a senior FDA official determines that a substantial scientific issue essential to determining the safety or effectiveness of the product was identified after the testing began. A SPA is not binding if new circumstances arise, and there is no guarantee that a study will ultimately be adequate to support an approval even if the study is subject to a SPA.

Orphan Drug Designation

The FDA may grant orphan drug designation to drugs and biological products intended to treat a rare disease or condition that affects fewer than 200,000 individuals in the United States, or if it affects more than 200,000 individuals in the United States and there is no reasonable expectation that the cost of developing and making the drug or biological product for this type of disease or condition will be recovered from sales in the United States. In the European Union, the EMA's Committee for Orphan Medicinal Products, or COMP, may recommend orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions affecting not more than 5 in 10,000 persons in the European Union Community. Additionally, designation is granted for products intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the drug in the European Union would be sufficient to justify the necessary investment in developing the drug or biological product. In addition, the COMP may only

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recommend orphan drug designation when the product in question offers a significant clinical benefit over existing approved products for the relevant indication. Following a positive opinion by the COMP, the European Commission adopts a decision granting orphan status. The COMP will reassess orphan status in parallel with EMA review of a marketing authorization application and orphan status may be withdrawn at that stage if it no longer fulfills the orphan criteria.

In the United States, orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages and user-fee waivers. In addition, if a product receives the first FDA approval for the indication for which it has orphan designation, the product is entitled to orphan drug exclusivity, which means the FDA may not approve any other application to market the same drug or biological product for the same indication for a period of 7 years, except in limited circumstances, such as a showing of clinical superiority over the product with orphan exclusivity.

In the European Union, orphan drug designation also entitles a party to financial incentives such as reduction of fees or fee waivers and 10 years of market exclusivity is granted following drug or biological product approval. During this period, regulators may not accept or approve any similar medicinal product, unless it offers a significant clinical benefit. This period may be reduced to 6 years if the orphan drug designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity.

Orphan drug designation must be requested before submitting an application for marketing approval. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

Pediatric Development

In the United States, Section 505A of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a, Pediatric Studies of Drugs) provides for an additional 6 months of marketing exclusivity for a drug if reports are filed of investigations studying the use of the drug product in a pediatric population in response to a written request from the FDA. Separate from this potential exclusivity benefit, NDAs and BLAs must contain data (or a proposal for post-marketing activity) to assess the safety and effectiveness of an investigational drug or biological product for the claimed indications in all relevant pediatric populations in order to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective. The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults or full or partial waivers if certain criteria are met. Discussions about pediatric development plans can be discussed with the FDA at any time, but usually occur any time between the end-of-phase 2 meeting and submission of the NDA or BLA.

For the EMA, a Pediatric Investigation Plan, and/or a request for waiver or deferral, is required for submission prior to submitting a marketing authorization application.

Authorization Procedures in the European Union

There are two types of authorization procedures for medicinal products in the European Union; the centralized authorization procedure and national authorization procedures.

Centralized procedure. The centralized procedure gives rise to marketing authorizations that are valid throughout the European Union and, by extension, in three European Economic Area, or EEA member states, Norway, Iceland and Liechtenstein. Applicants file marketing authorizations with the EMA, where they are reviewed by a relevant scientific committee, which is most likely the Committee for Medicinal Products for Human Use, or CHMP. The EMA forwards CHMP positive opinions to the European Commission, which uses them as the basis for a decision granting a marketing authorization. The centralized procedure is compulsory for human medicines that are: derived from biotechnology processes,

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such as recombinant DNA technology, controlled expression of genes in prokaryotes and eukaryotes and hybridoma and monoclonal antibody methods. It is also mandatory for products containing a new active substance indicated for the treatment of certain diseases, such as HIV/AIDS, cancer, diabetes, neurodegenerative disorders, viral diseases or autoimmune diseases and other immune dysfunctions, and officially designated orphan medicines. For medicines that do not fall within these categories, an applicant has the option of submitting an application for a centralized marketing authorization to the EMA, as long as the CHMP accepts that the medicine concerned is a significant therapeutic, scientific or technical innovation, or if its authorization would be in the interest of public health.

National authorization procedures. There are also two other possible routes to authorize medicinal products in more than one EU or EEA country, which are available for investigational drug products that fall outside the scope of the centralized procedure:

Decentralized procedure. Using the decentralized procedure, an applicant may apply for simultaneous authorization in more than one European Union country of medicinal products that have not yet been authorized in any European Union country and that do not fall within the mandatory scope of the centralized procedure. The applicant selects a so-called reference member state, or RMS, to take the lead in the review of the application. Other member states are expected to recognize the RMS decision, unless they identify a serious risk to public health. If the member states cannot resolve any such concerns between themselves, the matter is referred to the CHMP for an opinion and ultimately a binding European Commission decision.

Mutual recognition procedure. In the mutual recognition procedure, a medicine is first authorized in one European Union RMS, in accordance with the national procedures of that country. Following this, further marketing authorizations can be sought from other European Union countries in a procedure whereby the countries concerned agree to recognize the validity of the original, national marketing authorization. As in the decentralized procedure, these concerned member states must recognize the RMS approval unless they identify a serious risk to the public health. If the member states cannot reach a consensus between themselves, the matter can be referred to the CHMP.

Priority Review / Standard Review (United States) and Accelerated Review (European Union)

Based on results of the phase 3 clinical trial(s) submitted in an NDA or BLA, upon the request of an applicant a priority review designation may be granted to a product by the FDA, which sets the target date for FDA action on the application at 6 months. Priority review is given where preliminary estimates indicate that a product, if approved, has the potential to provide a safe and effective therapy where no satisfactory alternative therapy exists, or a significant improvement compared to marketed products is possible. If criteria are not met for priority review, the standard FDA review period is 10 months. Priority review designation does not change the scientific/medical standard for approval or the quality of evidence necessary to support approval.

Under the Centralized Procedure in the European Union, the maximum timeframe for the evaluation of a marketing authorization application is 210 days (excluding clock stops, when additional written or oral information is to be provided by the applicant in response to questions asked by the CHMP. Accelerated evaluation might be granted by the CHMP in exceptional cases, when a medicinal product is expected to be of a major public health interest, defined by three cumulative criteria: the seriousness of the disease (e.g. heavy disabling or life-threatening diseases) to be treated; the absence or insufficiency of an appropriate alternative therapeutic approach; and anticipation of high therapeutic benefit. In this circumstance, EMA ensures that the opinion of the CHMP is given within 150 days.

Pharmaceutical Coverage, Pricing and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any drug products for which we obtain regulatory approval. In the United States and markets in other countries, sales of any products for

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which we receive regulatory approval for commercial sale will depend in part on the availability of reimbursement from third party payors. Third party payors include government health administrative authorities, managed care providers, private health insurers and other organizations. The process for determining whether a payor will provide coverage for a drug product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the drug product. Third party payors may limit coverage to specific drug products on an approved list, or formulary, which might not include all of the FDA-approved drugs for a particular indication. Third party payors are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. We may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of our products, in addition to the costs required to obtain FDA approvals. Our product candidates may not be considered medically necessary or cost-effective. A payor's decision to provide coverage for a drug product does not imply that an adequate reimbursement rate will be approved. Adequate third party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

In recent years, Congress and some state legislatures have considered a number of proposals and have enacted laws that could effect major changes in the healthcare system, either nationally or at the state level.

The Medicare Part D outpatient prescription drug benefit went into effect in 2006. Such government payment for some of the costs of prescription drugs may increase demand for any products for which we receive marketing approval. However, coverage under Medicare Part D is provided primarily through private entities, which act as plan sponsors and negotiate price concessions from pharmaceutical manufacturers, thus limiting the payment we may be able to receive for our products for which we receive marketing approval, if any.

In 2010, Congress enacted sweeping health care reform legislation. This legislation is expected to substantially change the way that health care is financed by both governmental and private insurers and significantly affect the pharmaceutical industry. Among the provisions of the legislation are provisions governing enrollment in federal health care programs, increases in the rebates pharmaceutical manufacturers must pay to state Medicaid programs, expansion of the entities eligible for discounted 340B pricing, a manufacturer-funded 50% discount on prescriptions for branded products filled while the beneficiary is in the Medicare Part D coverage gap, and a significant annual fee on companies that manufacture or import branded prescription drug products. The legislation also includes substantial new provisions affecting compliance, including reporting provisions that relate to transfers of value to health care providers and to the distribution of product samples to health care providers. In addition, the federal government has been given additional enforcement authority.

Federal, state and local governments in the United States continue to consider legislation to limit the growth of healthcare costs, including the cost of prescription drugs. We are unable to predict the future course of federal or state health care legislation and regulations, including regulations that will be issued to implement provisions of the health care reform legislation. The recently enacted legislation and related and future developments could limit payments or sales volume for pharmaceuticals such as the drug candidates that we are developing or could impose taxes or other costs of doing business on pharmaceutical manufacturers.

Different pricing and reimbursement schemes exist in other countries. In the European Community, governments influence the price of pharmaceutical products through their pricing and reimbursement rules and control of national health care systems that fund a large part of the cost of those products to consumers. Some jurisdictions operate positive and negative list systems under which products may only be marketed once a reimbursement price has been agreed. To obtain reimbursement or pricing approval, some of these countries may require the completion of clinical trials that compare the cost-effectiveness of a particular product candidate to currently available therapies. Other member states allow companies to fix their own prices for medicines, but monitor and control company profits. The downward pressure on health care costs in general, particularly prescription drugs, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross-border imports from low-priced markets exert a commercial pressure on pricing within a country.

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The marketability of any products for which we receive regulatory approval for commercial sale may suffer if the government and third party payors fail to provide adequate coverage and reimbursement. In addition, an increasing emphasis on managed care in the United States has increased and we expect will continue to increase the pressure on pharmaceutical pricing. Coverage policies and third party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Other Healthcare Laws and Compliance Requirements

In the United States, our activities are potentially subject to regulation by various federal, state and local authorities in addition to the FDA, including the Centers for Medicare and Medicaid Services, other divisions of the U.S. Department of Health and Human Services (e.g., the Office of Inspector General), the Department of Veterans Affairs, the U.S. Department of Justice and individual U.S. Attorney offices within the Department of Justice, and state and local governments. For example, sales, marketing and scientific/educational grant programs must comply with the anti-fraud and abuse provisions of the Social Security Act, the False Claims Act, the privacy provisions of the Health Insurance Portability and Accountability Act, or HIPAA, and similar state laws, each as amended. Pricing and rebate programs must comply with the Medicaid rebate requirements of the Omnibus Budget Reconciliation Act of 1990 and the Veterans Health Care Act of 1992, each as amended. If products are made available to authorized users of the Federal Supply Schedule of the General Services Administration, additional laws and requirements apply. Under the Veterans Health Care Act, or VHCA, drug companies are required to offer certain drugs at a reduced price to a number of federal agencies including U.S. Department of Veterans Affairs and U.S. Department of Defense, the Public Health Service and certain private Public Health Service designated entities in order to participate in other federal funding programs including Medicare and Medicaid. Participation under the VHCA requires submission of pricing data and calculation of discounts and rebates pursuant to complex statutory formulas, as well as the entry into government procurement contracts governed by the Federal Acquisition Regulations. In addition, legislative changes may require that discounted prices be offered for certain U.S. Department of Defense purchases for its TRICARE retail pharmacy program via a rebate system.

In order to distribute products commercially, we must comply with state laws that require the registration of manufacturers and wholesale distributors of pharmaceutical products in a state, including, in certain states, manufacturers and distributors who ship products into the state even if such manufacturers or distributors have no place of business within the state. Some states also impose requirements on manufacturers and distributors to establish the pedigree of product in the chain of distribution, including some states that require manufacturers and others to adopt new technology capable of tracking and tracing product as it moves through the distribution chain. Several states have enacted legislation requiring pharmaceutical companies to establish marketing compliance programs, file periodic reports with the state, make periodic public disclosures on sales, marketing, pricing, clinical trials and other activities, and/or register their sales representatives, as well as to prohibit pharmacies and other healthcare entities from providing certain physician prescribing data to pharmaceutical companies for use in sales and marketing, and to prohibit certain other sales and marketing practices. All of our activities are potentially subject to federal and state consumer protection and unfair competition laws.

Employees

As of December 31, 2010, we had 147 employees worldwide. None of our employees is represented by a labor union or is covered by a collective bargaining agreement. We consider our relationship with our employees to be good.

Legal Proceedings

We are not currently a party to any material legal proceedings.

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Research and Development Costs

Our research and development costs were \$86.3 million in 2010, \$51.8 million in 2009, and \$41.8 million in 2008. These costs consist of the cost of our own independent research and development efforts and the costs associated with collaborative research and development and in-licensing arrangements. Research and development costs, including upfront fees and milestones paid to collaboration partners, are expensed as incurred if the underlying products have not received regulatory approval and have no future alternative use.

Executive Officers

The following table lists the positions, names and ages of our executive officers as of March 1, 2011:

Executive Officers

Tuan Ha-Ngoc	58	Chief Executive Officer, President and Director
David Johnston	55	Chief Financial Officer
Elan Ezickson	47	Executive Vice President, Chief Business Officer
William Slichenmyer, M.D., Sc.M.	53	Chief Medical Officer
Michael P. Bailey	45	Chief Commercial Officer
Jeno Gyuris, Ph.D.	51	Senior Vice President, Head of Research

Tuan Ha-Ngoc has served as President and Chief Executive Officer of our company and as a member of our Board of Directors since June 2002. From 1999 to 2002, he was co-founder, President and Chief Executive Officer of deNovis, Inc., an enterprise-scale software development company for the automation of healthcare administrative functions. From 1998 to 1999, Mr. Ha-Ngoc was Corporate Vice President of Strategic Development for Wyeth, following Wyeth's acquisition of Genetics Institute, where Mr. Ha-Ngoc served as Executive Vice President with responsibility for corporate development, commercial operations and European and Japanese operations. Mr. Ha-Ngoc serves on the Board of Directors of Human Genome Sciences, Inc. as well as on the boards of a number of academic and nonprofit organizations, including the Harvard School of Dental Medicine, the Tufts School of Medicine, the MIT Koch Institute of Integrative Cancer Research, the Boston Philharmonic Orchestra, and the International Institute of Boston. Mr. Ha-Ngoc served on the Board of Directors of ArQule, Inc., from 2002 until 2006. He holds an M.B.A. from INSEAD and an M.A. in pharmacy from the University of Paris, France. We believe that Mr. Ha-Ngoc's qualifications to serve on our Board of Directors include his position as our chief executive officer and his significant experience in the cancer research field and corporate strategy development, including his executive leadership roles at global pharmaceutical companies, and his experiences in commercializing potential drug candidates, including his commercialization experience in North America, Europe and Japan.

David Johnston has served as our Chief Financial Officer since October 2007. From 1998 to 2007, he served as Senior Vice President of Corporate Finance at Genzyme Corporation. Mr. Johnston sits on the Board of Directors of Tissue Banks International. Mr. Johnston holds a B.S. from Washington and Lee University and an M.B.A. from the University of Michigan.

Elan Ezickson was named Executive Vice President effective as of July 1, 2010 and has served as our Chief Business Officer since April 2003. From 1994 to 2003, he worked at Biogen in roles that included President of Biogen Canada, Program Executive and Associate General Counsel. Mr. Ezickson sits on the Board of Directors of the Greater Boston Food Bank. Mr. Ezickson holds a B.A. in Political Science from Yale University and a J.D. from the Columbia University School of Law.

William Slichenmyer, M.D., Sc.M. has served as our Chief Medical Officer since September 2009. Prior to joining our company, Dr. Slichenmyer served as Chief Medical Officer at Merrimack Pharmaceuticals from 2007 to September 2009. From 2000 to 2007, Dr. Slichenmyer worked at Pfizer Inc. in roles that included Global Head of Oncology Clinical Development as well as positions in medical affairs and regulatory affairs. Dr. Slichenmyer holds a B.A. and M.D. from Case Western Reserve University and an Sc.M. in clinical investigation from Johns Hopkins Oncology Center.

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Michael P. Bailey has served as our Chief Commercial Officer since September 2010. Prior to joining our company, Mr. Bailey served as Senior Vice President, Business Development and Chief Commercial Officer at Synta Pharmaceuticals from 2008 to September 2010. From 1999 to 2008, Mr. Bailey worked at ImClone, leading their commercial organization, most recently as Senior Vice President of Commercial Operations. Prior to his role at ImClone, Mr. Bailey managed the cardiovascular development portfolio at Genentech, Inc. from 1997 to 1999. Mr. Bailey started his career in the pharmaceutical industry as part of Smith-Kline Beecham's Executive Marketing Development Program, where he held a variety of commercial roles from 1992 to 1997, including sales, strategic planning, and product management. Mr. Bailey received a B.S. in psychology from St. Lawrence University and an M.B.A. in international marketing from the University of Notre Dame Graduate School of Business.

Jeno Gyuris, Ph.D. was named Senior Vice President, Head of Research in January 2010, and oversees all our research activities. Dr. Gyuris joined our company in January 2003 and served as our Vice President, Molecular Technologies until January 2007 and as our Senior Vice President, Drug Discovery from January 2007 to January 2010. From 1993 to 2002, Dr. Gyuris worked at GPC Biotech AG, formerly Mitotix Inc., where he held positions of increasing responsibility, most recently Vice President of Molecular Technologies. Dr. Gyuris has received several research fellowships in Europe and the United States, and is the author of numerous patents and publications. Dr. Gyuris received his Ph.D. from University of Szeged, Szeged, Hungary.

Available Information

We file reports and other information with the SEC as required by the Securities Exchange Act of 1934, as amended, which we refer to as the Exchange Act. You can find, copy and inspect information we file at the SEC's public reference room, which is located at 100 F Street, N.E., Room 1580, Washington, DC 20549. Please call the SEC at 1-800-SEC-0330 for more information about the operation of the SEC's public reference room. You can review our electronically filed reports and other information that we file with the SEC on the SEC's web site at <http://www.sec.gov>.

We were incorporated under the laws of the State of Delaware on October 19, 2001 as GenPath Pharmaceuticals, Inc. and changed our name to AVEO Pharmaceuticals, Inc. on March 1, 2005. Our principal executive offices are located at 75 Sidney Street, Cambridge, Massachusetts, 02139, and our telephone number is (617) 299-5000. Our Internet website is <http://www.aveopharma.com>. We make available free of charge through our website our annual report on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and amendments to those reports filed or furnished pursuant to Sections 13(a) and 15(d) of the Exchange Act. We make these reports available through our website as soon as reasonably practicable after we electronically file such reports with, or furnish such reports to, the SEC. In addition, we regularly use our website to post information regarding our business, product development programs and governance, and we encourage investors to use our website, particularly the information in the section entitled "Investors/Media," as a source of information about us.

The foregoing references to our website are not intended to, nor shall they be deemed to, incorporate information on our website into this report by reference.

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ITEM 1A. Risk Factors

Our business is subject to numerous risks. We caution you that the following important factors, among others, could cause our actual results to differ materially from those expressed in forward-looking statements made by us or on our behalf in filings with the SEC, press releases, communications with investors and oral statements. Any or all of our forward-looking statements in this Annual Report on Form 10-K and in any other public statements we make may turn out to be wrong. They can be affected by inaccurate assumptions we might make or by known or unknown risks and uncertainties. Many factors mentioned in the discussion below will be important in determining future results. Consequently, no forward-looking statement can be guaranteed. Actual future results may differ materially from those anticipated in forward-looking statements. We undertake no obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise. You are advised, however, to consult any further disclosure we make in our reports filed with the SEC.

Risks Related to Development, Clinical Testing and Regulatory Approval of Our Drug Candidates

We are dependent on the success of our lead drug candidate, tivozanib, which is in phase 3 development.

To date, we have invested a significant portion of our efforts and financial resources in the research and development of tivozanib. We are currently conducting our phase 3 registration clinical trial for tivozanib, referred to as TIVO-1, as well as a phase 2 clinical trial and five phase 1 clinical trials, four of which focus on tivozanib in combination with other known anti-cancer agents.

Our near-term prospects, including our ability to finance our company and to generate strategic partnerships and revenues, will depend heavily on the successful development and commercialization of tivozanib. All of our other potential product candidates, with the exception of ficlatuzumab, are in the preclinical research stage. The clinical and commercial success of tivozanib will depend on a number of factors, including the following:

successful completion of our phase 3 clinical trial and timely enrollment in, and completion of, our other on-going or planned clinical trials;

our ability to demonstrate to the satisfaction of the U.S. Food and Drug Administration, or FDA, or equivalent foreign regulatory agencies, tivozanib's safety and efficacy through current and future clinical trials, including without limitation TIVO-1;

the prevalence and severity of adverse side effects;

timely receipt of necessary marketing approvals from the FDA and similar foreign regulatory authorities;

achieving and maintaining compliance with all regulatory requirements applicable to tivozanib;

the availability, relative cost, safety and efficacy of alternative and competing treatments;

the effectiveness of our marketing, sales and distribution strategies and operations, and those of Astellas, our strategic collaboration partner for development and commercialization of tivozanib;

the ability of our third-party manufacturers to manufacture clinical trial and commercial supplies of tivozanib and to develop, validate and maintain a commercially viable manufacturing process that is compliant with current good manufacturing practices, or cGMP;

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our ability, and the ability of Astellas, to successfully obtain third party reimbursement and generate commercial demand that result in sales of tivozanib, assuming applicable regulatory approvals are obtained;

our ability to avoid third party patent interference or patent infringement claims;

acceptance of tivozanib as safe and effective by patients, the medical community and third-party payors; and

a continued acceptable safety profile of the product following approval.

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Many of these factors are beyond our control. Accordingly, we cannot assure you that we, or our strategic partner, will ever be able to generate revenues through the sale of tivozanib. If we, or our strategic partner, are not successful in commercializing tivozanib, or are significantly delayed in doing so, our business will be materially harmed and the price of our common stock could substantially decline.

Positive results in our phase 2 clinical trial of tivozanib may not be predictive of the results in our phase 3 clinical trial. If the results of our phase 3 clinical trial are not positive, or are not sufficient for approval of tivozanib, our business will be adversely affected.

Positive results in early clinical trials of a drug candidate may not be replicated in later clinical trials. A number of companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials even after achieving promising results in earlier-stage development. Although the results of our phase 2 clinical trial of tivozanib for the treatment of advanced RCC were positive, we cannot assure you that the phase 3 clinical trial for the treatment of advanced RCC will achieve positive results. A number of factors could contribute to a lack of positive results in our phase 3 clinical trial of tivozanib.

For example, in our phase 2 clinical trial, we compared tivozanib to treatment with placebo. In our phase 3 clinical trial, the primary endpoint is a comparison of progression-free survival of patients treated with tivozanib to the progression-free survival of patients treated with Nexavar. Nexavar is a VEGF receptor inhibitor which has been approved by the FDA and the European Medicines Agency, or the EMA, for the treatment of advanced RCC, as well as the treatment of hepatocellular carcinoma. Based on our discussions with the FDA and the EMA, we set the number of patients to be enrolled in the clinical trial at a number we expect will be sufficient to demonstrate that a difference in progression-free survival of three months or more between the treatment arms would be statistically significant. The FDA has advised us that the results of the phase 3 clinical trial will need to show not only that patients treated with tivozanib have a statistically significant improvement in progression-free survival as compared to patients treated with Nexavar, but also that the improvement in progression-free survival of patients treated with tivozanib is clinically meaningful in the context of the safety of the drug. It is not clear how much of an improvement in progression-free survival will be required in order for it to be deemed clinically meaningful in the context of the safety of the drug. The FDA and other regulatory authorities will have substantial discretion in evaluating the results of our phase 3 clinical trial, including with respect to what constitutes a clinically meaningful improvement in progression-free survival. Overall survival is a secondary endpoint in our phase 3 clinical trial. Based on our discussions with the FDA, we do not expect the FDA to require that we show a statistically significant improvement in overall survival in patients treated with tivozanib in order to obtain approval by the FDA; however, if the overall survival data are not positive, it may influence how the FDA and other regulatory authorities interpret other data from our phase 3 clinical trial. We did not gather data on overall survival in our phase 2 clinical trial of tivozanib.

We cannot be certain as to what type and how many clinical trials the FDA, or equivalent foreign regulatory agencies, will require us to conduct before we may successfully gain approval to market tivozanib. Prior to approving a new drug, the FDA generally requires that the efficacy of the drug be demonstrated in two adequate and well-controlled clinical trials. In some situations, the FDA approves drugs on the basis of a single well-controlled clinical trial. Based on our discussions with the FDA and the EMA, we believe we will be required to conduct only a single phase 3 clinical trial of tivozanib in advanced RCC. All of the VEGF inhibitor drugs approved by the FDA and the EMA to date in advanced RCC, including Votrient, which was approved by the FDA in October 2009, have been approved on the basis of a single phase 3 clinical trial. However, if the FDA or EMA determines that our phase 3 clinical trial results are not statistically significant and do not demonstrate a clinically meaningful benefit and an acceptable safety profile, or if the FDA or EMA requires us to conduct additional phase 3 clinical trials of tivozanib in order to gain approval, we will incur significant additional development costs, commercialization of tivozanib would be prevented or delayed and our business would be adversely affected.

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If we do not obtain regulatory approval for tivozanib, ficlatuzumab or any other product candidates, our business will be adversely affected.

Tivozanib, ficlatuzumab and any other product candidate we seek to develop will be subject to extensive governmental regulations relating to, among other things, development, clinical trials, manufacturing and commercialization. In order to obtain regulatory approval for the commercial sale of any product candidate, we must demonstrate through extensive preclinical studies and clinical trials that the product candidate is safe and effective for use in each target indication, and that our production process yields a consistent and stable product. This process can take many years to complete, requiring the expenditure of substantial resources with highly uncertain results. We or our strategic partners may never obtain regulatory approval for tivozanib, ficlatuzumab or any other product candidate we may develop.

We have completed a phase 2 clinical trial of our lead product candidate, tivozanib, and are currently conducting a phase 3 clinical trial of tivozanib for the treatment of RCC. We are also conducting phase 1b clinical trials of tivozanib in various combinations and dosing regimens in RCC and additional solid tumor indications, including breast cancer and colorectal cancer. In addition to tivozanib, we have a pipeline of monoclonal antibodies derived from our Human Response Platform, a novel method of building preclinical models of human cancer, which are intended to more accurately represent cancer biology in patients. Our first product candidate derived from our Human Response Platform, ficlatuzumab, has entered a phase 2 clinical trial for non-small cell lung cancer. The results to date from preclinical studies, our phase 1 and phase 2 clinical trials of tivozanib and our phase 1 clinical trials of ficlatuzumab may not be predictive of results in preclinical studies and clinical trials currently in process or that we may initiate in the future. A failure of one or more preclinical or clinical trials can occur at any stage of testing. Moreover, there can be no assurance that we will demonstrate the required safety and efficacy to obtain regulatory approvals for any of our product candidates.

Even though tivozanib has been generally well-tolerated in the limited number of patients who have been treated with it, there is no guarantee that unacceptable side effects or other risks will not occur with the exposure of a larger number of patients. If tivozanib, ficlatuzumab or any other product candidate is not shown to be safe and effective in humans through clinical trials, we or our strategic partners will not be able to obtain regulatory approval for such product candidate, and the resulting delays in developing other product candidates and conducting related preclinical studies and clinical trials, as well as the potential need for additional financing, would have a material adverse effect on our business, financial condition and results of operations.

If we are not successful in discovering, developing and commercializing additional product candidates, our ability to expand our business and achieve our strategic objectives would be impaired.

Although a substantial amount of our efforts will focus on the continued clinical testing and potential approval of tivozanib as well as the continued development of ficlatuzumab, a key element of our strategy is to discover, develop and commercialize a portfolio of antibody-based products. We are seeking to do so through our internal research programs and intend to explore strategic partnerships for the development of new products. All of our other potential product candidates remain in the discovery and preclinical study stages. Research programs to identify product candidates require substantial technical, financial and human resources, whether or not any product candidates are ultimately identified. Our research programs may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development for many reasons, including the following:

the research methodology used may not be successful in identifying potential product candidates;

competitors may develop alternatives that render our product candidates obsolete;

a product candidate may on further study be shown to have harmful side effects or other characteristics that indicate it is unlikely to be effective or otherwise does not meet applicable regulatory criteria;

a product candidate may not be capable of being produced in commercial quantities at an acceptable cost, or at all; and

a product candidate may not be accepted as safe and effective by patients, the medical community or third-party payors.

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Any failure or delay in completing clinical trials for our product candidates may prevent us from obtaining regulatory approval or commercializing product candidates on a timely basis, or at all, which would require us to incur additional costs and delay receipt of any product revenue.

We cannot predict whether we will encounter problems with any of our ongoing or planned clinical trials that will cause us or regulatory authorities to delay, suspend or terminate those clinical trials. The completion of clinical trials for product candidates may be delayed or halted for many reasons, including:

delays or failure in reaching agreement on acceptable clinical trial contracts or clinical trial protocols with prospective sites;

failure of our third-party contractors or our investigators to comply with regulatory requirements or otherwise meet their contractual obligations in a timely manner;

delays or failure in obtaining the necessary approvals from regulators or institutional review boards in order to commence a clinical trial at a prospective trial site, or their suspension or termination of a clinical trial once commenced;

our inability to manufacture or obtain from third parties materials sufficient to complete our preclinical studies and clinical trials;

delays in patient enrollment, and variability in the number and types of patients available for clinical trials, or high drop-out rates of patients in our clinical trials;

difficulty in maintaining contact with patients after treatment, resulting in incomplete data;

poor effectiveness of our product candidates during clinical trials;

safety issues, including serious adverse events associated with our product candidates;

governmental or regulatory delays and changes in regulatory requirements, policy and guidelines; or

varying interpretations of data by the FDA and similar foreign regulatory agencies.

Clinical trials often require the enrollment of large numbers of patients, and suitable patients may be difficult to identify and recruit. Our ability to enroll sufficient numbers of patients in our clinical trials depends on many factors, including the size of the patient population, the nature of the protocol, the proximity of patients to clinical sites, the eligibility criteria for the trial, competing clinical trials and the availability of approved effective drugs. In addition, patients may withdraw from a clinical trial for a variety of reasons. If we fail to enroll and maintain the number of patients for which the clinical trial was designed, the statistical power of that clinical trial may be reduced which would make it harder to demonstrate that the product candidate being tested in such clinical trial is safe and effective. Additionally, we may not be able to enroll a sufficient number of qualified patients in a timely or cost-effective manner.

We, the FDA, other applicable regulatory authorities or institutional review boards may suspend or terminate clinical trials of a product candidate at any time if we or they believe the patients participating in such clinical trials are being exposed to unacceptable health risks or for other reasons.

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Significant clinical trial delays could allow our competitors to obtain marketing approval before we do or shorten the patent protection period during which we may have the exclusive right to commercialize our product candidates. Our product development costs also will increase if we experience delays in completing clinical trials. In addition, it is impossible to predict whether legislative changes will be enacted, or whether FDA regulations, guidance or interpretations will be changed, or what the impact of such changes, if any, may be. If we experience any such problems, we may not have the financial resources to continue development of the product candidate that is affected or the development of any of our other product candidates.

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Even if we receive regulatory approval for any of our product candidates, we will be subject to ongoing FDA requirements and continued regulatory review, which may result in significant additional expense. Additionally, our product candidates, if approved, could be subject to labeling and other restrictions and market withdrawal and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our products.

Any regulatory approvals that we or our strategic partners receive for our product candidates may also be subject to limitations on the approved indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including phase 4 clinical trials, and surveillance to monitor the safety and efficacy of the product candidate. In addition, if the FDA approves any of our product candidates, the manufacturing processes, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion and recordkeeping for the product will be subject to extensive and ongoing regulatory requirements. These requirements include submissions of safety and other post-marketing information and reports, registration, as well as continued compliance with cGMP and good clinical practices, or GCP, for any clinical trials that we conduct post-approval. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with our third-party manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in, among other things:

restrictions on the marketing or manufacturing of the product, withdrawal of the product from the market, or voluntary or mandatory product recalls;

fines, warning letters or holds on clinical trials;

refusal by the FDA to approve pending applications or supplements to approved applications filed by us or our strategic partners, or suspension or revocation of product license approvals;

product seizure or detention, or refusal to permit the import or export of products; and

injunctions or the imposition of civil or criminal penalties.

The FDA's policies may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability, which would adversely affect our business.

Failure to obtain regulatory approval in jurisdictions outside the United States will prevent us from marketing our products abroad.

We intend to market our products, if approved, in international markets, which will require separate regulatory approvals and compliance with numerous and varying regulatory requirements. The approval procedures vary among countries and may involve requirements for additional testing, and the time required to obtain approval may differ from that required to obtain FDA approval. In addition, in many countries outside the United States, a product candidate must be approved for reimbursement before it can be approved for sale in that country. In some cases, the price that we intend to charge for our product is also subject to approval. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one foreign regulatory authority does not ensure approval by regulatory authorities in other foreign countries or jurisdictions or by the FDA. The foreign regulatory approval process may include all of the risks associated with obtaining FDA approval. We may not obtain foreign regulatory approvals on a timely basis, if at all. We and our strategic partners may not be able to file for regulatory approvals and may not receive necessary approvals to commercialize our products in any market.

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Risks Related to Our Financial Position and Capital Requirements

We anticipate that we will continue to incur significant operating costs for the foreseeable future. We may never achieve or sustain profitability, which would depress the market price of our common stock.

We have incurred net losses since our inception, including net losses of \$58.8 million, \$44.1 million and \$32.5 million for the years ended December 31, 2010, 2009 and 2008, respectively. As of December 31, 2010, we had an accumulated deficit of \$236.5 million. We do not know whether or when we will achieve or sustain profitability. To date, we have not commercialized any products or generated any revenues from the sale of products. Our losses have resulted principally from costs incurred in our discovery and development activities. We anticipate that we will continue to incur significant operating costs over the next several years as we execute our plan to expand our discovery, research, development and commercialization activities, including the phase 3 clinical development and planned commercialization of our lead product candidate, tivozanib, and the continued clinical development of our phase 2 product candidate, ficlatuzumab, to which we recently regained rights from Merck.

If we do not successfully develop and obtain regulatory approval for our existing and future pipeline product candidates and effectively manufacture, market and sell any product candidates that are approved, we may never generate product sales, and even if we do generate product sales, we may never achieve or sustain profitability on a quarterly or annual basis. Our failure to become and remain profitable would depress the market price of our common stock and could impair our ability to raise capital, expand our business, diversify our product offerings or continue our operations.

We will require substantial additional financing to achieve our goals, and a failure to obtain this necessary capital when needed could force us to delay, limit, reduce or terminate our product development or commercialization efforts.

Since our inception, most of our resources have been dedicated to the discovery, preclinical and clinical development of our product candidates. In particular, we are currently conducting a phase 3 and phase 2 clinical trial of tivozanib, with which we share expenses with Astellas, and a phase 2 clinical trial of ficlatuzumab, which will require substantial funds to complete. We believe that we will continue to expend substantial resources for the foreseeable future developing tivozanib, ficlatuzumab and other new and existing antibody product candidates. These expenditures will include costs associated with research and development, acquiring new technologies, conducting preclinical and clinical trials, obtaining regulatory approvals and manufacturing products, as well as marketing and selling any products approved for sale. In addition, other unanticipated costs may arise. Because the outcome of our planned and anticipated clinical trials is highly uncertain, we cannot reasonably estimate the actual amounts necessary to successfully complete the development and commercialization of our product candidates.

We believe that our existing cash and cash equivalents, marketable securities, committed research and development funding and milestone payments that we expect to receive under our existing strategic partnership and license agreements, including the upfront payments we received under the Astellas agreement, will allow us to fund our operating plan through 2012. However, our operating plan may change as a result of many factors currently unknown to us, and we may need to seek additional funds sooner than planned, through public or private equity or debt financings or other sources, such as strategic partnerships. In addition, we may seek additional capital due to favorable market conditions or strategic considerations even if we believe we have sufficient funds for our current or future operating plans.

Our future capital requirements depend on many factors, including:

the number and characteristics of the product candidates we pursue;

the scope, progress, results and costs of researching and developing our product candidates, and conducting preclinical and clinical trials;

the timing of, and the costs involved in, obtaining regulatory approvals for our product candidates;

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the cost of commercialization activities if any of our product candidates are approved for sale, including marketing, sales and distribution costs;

the cost of manufacturing our product candidates and any products we successfully commercialize;

our ability to establish and maintain strategic partnerships, licensing or other arrangements and the financial terms of such agreements;

the costs involved in preparing, filing, prosecuting, maintaining, defending and enforcing patent claims, including litigation costs and the outcome of such litigation; and

the timing, receipt and amount of sales of, or royalties on, our future products, if any.

Additional funds may not be available when we need them, on terms that are acceptable to us, or at all. If adequate funds are not available to us on a timely basis, we may be required to:

delay, limit, reduce or terminate preclinical studies, clinical trials or other development activities for one or more of our product candidates;

delay, limit, reduce or terminate our research and development activities; or

delay, limit, reduce or terminate our establishment of sales and marketing capabilities or other activities that may be necessary to commercialize our product candidates.

Raising additional capital may cause dilution to our existing stockholders, restrict our operations or require us to relinquish rights to our technologies or product candidates.

We may seek additional capital through a combination of private and public equity offerings, debt financings, strategic partnerships and alliances and licensing arrangements. To the extent that we raise additional capital through the sale of equity or convertible debt securities, stockholders will be diluted, and the terms may include liquidation or other preferences that adversely affect stockholders' rights. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take certain actions, such as incurring debt, making capital expenditures or declaring dividends. If we raise additional funds through strategic partnerships and alliances and licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies or product candidates, or grant licenses on terms that are not favorable to us. If we are unable to raise additional funds through equity or debt financing when needed, we may be required to delay, limit, reduce or terminate our product development or commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

A substantial portion of our future revenues may be dependent upon our agreements with Astellas, OSI Pharmaceuticals and Biogen Idec.

Our success will depend in significant part on our ability to attract and maintain strategic partners and strategic relationships to support the development and commercialization of our products. We currently expect that a substantial portion of our future revenues may be dependent upon our strategic partnerships with Astellas, OSI Pharmaceuticals and Biogen Idec. Under each of these strategic partnerships, our strategic partners have significant development and commercialization responsibilities with respect to anticipated therapeutics to be developed and sold. If these strategic partners were to terminate their agreements with us, fail to meet their obligations or otherwise decrease their level of efforts, allocation of resources or other commitments under these agreements, our future revenues could be negatively impacted and the development and commercialization of our product candidates would be interrupted. In addition, if some or any of the development, regulatory and commercial milestones are not achieved or if certain net sales thresholds are not achieved, as set forth in the respective agreements, we will not fully realize the expected economic benefits of the agreements. Further, the achievement of certain of the milestones under these strategic

partnership agreements will depend on factors that are outside of our control and most are not expected to be achieved for several years, if at all. Any failure to successfully maintain our strategic partnership agreements could materially and adversely affect our ability to generate revenues.

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For a discussion of additional risks that we face with respect to our strategic partnership agreements, see [If any of our current strategic partners fails to perform its obligations or terminates its agreement with us, the development and commercialization of the product candidates under such agreement could be delayed or terminated and our business could be substantially harmed](#) beginning on page 68.

Fluctuations in our quarterly operating losses could adversely affect the price of our common stock.

Our quarterly operating losses may fluctuate significantly. Some of the factors that may cause our operating losses to fluctuate on a period-to-period basis include:

the status of our preclinical and clinical development programs;

the level of expenses incurred in connection with our preclinical and clinical development programs;

any intellectual property infringement lawsuit or other litigation in which we may become involved;

the implementation or termination of collaboration, licensing, manufacturing or other material agreements with third parties, and non-recurring revenue or expenses under any such agreement; and

compliance with regulatory requirements.

Period-to-period comparisons of our historical and future financial results may not be meaningful, and investors should not rely on them as an indication of future performance. Our fluctuating losses may fail to meet the expectations of securities analysts or investors. Our failure to meet these expectations may cause the price of our common stock to decline.

Unstable market and economic conditions may have serious adverse consequences on our business, financial condition and stock price.

As widely reported, global credit and financial markets have been experiencing extreme disruptions over the past several years, including severely diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates, and uncertainty about economic stability. There can be no assurance that further deterioration in credit and financial markets and confidence in economic conditions will not occur. Our general business strategy may be adversely affected by the current adverse economic conditions and volatile business environment and continued unpredictable and unstable market conditions. If the current equity and credit markets deteriorate further, or do not improve, it may make any necessary debt or equity financing more difficult, more costly, and more dilutive. Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse effect on our growth strategy, financial performance and stock price and could require us to delay or abandon clinical development plans. In addition, there is a risk that one or more of our current service providers, manufacturers and other partners may not survive these difficult economic times, which could directly affect our ability to attain our operating goals on schedule and on budget.

At December 31, 2010, we had \$140.2 million of cash, cash equivalents and marketable securities consisting of money market funds, U.S. treasuries, U.S. government agency securities, corporate debt and commercial paper. As of the date of this report, we are not aware of any downgrades, material losses, or other significant deterioration in the fair value of our cash equivalents or marketable securities. However, no assurance can be given that further deterioration in conditions of the global credit and financial markets would not negatively impact our current portfolio of cash equivalents or marketable securities or our ability to meet our financing objectives. Further dislocations in the credit market may adversely impact the value and/or liquidity of marketable securities owned by us.

There is a possibility that our stock price may decline, due in part to the volatility of the stock market and the general economic downturn.

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Risks Related to Our Business and Industry

Because we have a short operating history, there is a limited amount of information about us upon which you can evaluate our business and prospects.

Our operations began in October 2001 and we have only a limited operating history upon which you can evaluate our business and prospects. In addition, as an early stage company, we have limited experience and have not yet demonstrated an ability to successfully overcome many of the risks and uncertainties frequently encountered by companies in new and rapidly evolving fields, particularly in the biopharmaceutical area. For example, to execute our business plan, we will need to successfully:

execute product development activities;

obtain required regulatory approvals for the development and commercialization of our product candidates;

build and maintain a strong intellectual property portfolio;

build and maintain robust sales, distribution and marketing capabilities;

obtain reimbursement and gain market acceptance for our products;

develop and maintain successful strategic relationships and partnerships; and

manage our spending as costs and expenses increase due to clinical trials, regulatory approvals and commercialization.

If we are unsuccessful in accomplishing these objectives, we may not be able to develop product candidates, raise capital, expand our business or continue our operations.

We face substantial competition, which may result in others discovering, developing or commercializing products before, or more successfully, than we do.

Our future success depends on our ability to demonstrate and maintain a competitive advantage with respect to the design, development and commercialization of product candidates. Our objective is to design, develop and commercialize new products with superior efficacy, convenience, tolerability and safety. We expect any product candidate that we commercialize with our strategic partners or on our own will compete with existing, market-leading products. For example, we anticipate that tivozanib, if approved for the treatment of advanced RCC, would compete with angiogenesis inhibitors and mTOR inhibitors that are currently approved for the treatment of advanced RCC, such as Avastin, marketed by Roche Laboratories, Inc., Nexavar, marketed by Onyx Pharmaceuticals, Inc. and Bayer HealthCare AG, Sutent, marketed by Pfizer Inc., Votrient, marketed by GlaxoSmithKline plc, Torisel, marketed by Pfizer, and Afinitor, marketed by Novartis Pharmaceuticals Corporation, and other therapies in development.

Many of our potential competitors have substantially greater financial, technical and personnel resources than we have. In addition, many of these competitors have significantly greater commercial infrastructures than we have. We will not be able to compete successfully unless we successfully:

design and develop products that are superior to other products in the market;

attract qualified scientific, medical, sales and marketing and commercial personnel;

obtain patent and/or other proprietary protection for our processes and product candidates;

obtain favorable reimbursement, formulary and guideline status;

obtain required regulatory approvals; and

collaborate with others in the design, development and commercialization of new products.

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Established competitors may invest heavily to quickly discover and develop novel compounds that could make our product candidates obsolete. In addition, any new product that competes with an approved product must demonstrate compelling advantages in efficacy, convenience, tolerability and safety in order to overcome price competition and to be commercially successful. If we are not able to compete effectively against our current and future competitors, our business will not grow and our financial condition and operations will suffer.

If we fail to attract and keep senior management and key scientific personnel, we may be unable to successfully develop our product candidates, conduct our clinical trials and commercialize our product candidates.

Our success depends in part on our continued ability to attract, retain and motivate highly qualified management, clinical and scientific personnel. We are highly dependent upon our senior management, particularly Tuan Ha-Ngoc, our President and Chief Executive Officer, Elan Ezickson, our Executive Vice President and Chief Business Officer, David Johnston, our Chief Financial Officer, William Slichenmyer, our Chief Medical Officer, Michael Bailey, our Chief Commercial Officer, and Jeno Gyuris, our Senior Vice President, Head of Research, as well as other senior scientists on our management team. Although none of these individuals has informed us to date that he intends to retire or resign in the near future, the loss of services of any of these individuals or one or more of our other members of senior management could delay or prevent the successful development of our product pipeline, completion of our planned clinical trials or the commercialization of our product candidates. We do not carry key person insurance covering any members of our senior management. Although we have entered into an employment agreement and a severance and change in control agreement with Tuan Ha-Ngoc, and severance and change in control agreements with each of Elan Ezickson, David Johnston, William Slichenmyer, Michael Bailey and Jeno Gyuris, these agreements do not provide for a fixed term of service.

Although we have not historically experienced unique difficulties attracting and retaining qualified employees, we could experience such problems in the future. For example, competition for qualified personnel in the biotechnology and pharmaceuticals field is intense. We will need to hire additional personnel as we expand our clinical development and commercial activities. We may not be able to attract and retain quality personnel on acceptable terms.

Our employees may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements and insider trading.

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with FDA regulations, to provide accurate information to the FDA, to comply with manufacturing standards we have established, to comply with federal and state health-care fraud and abuse laws and regulations, to report financial information or data accurately or to disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Employee misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. We have adopted a Code of Business Conduct and Ethics, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions.

In addition, during the course of our operations, our directors, executives and employees may have access to material, nonpublic information regarding our business, our results of operations or potential transactions we are

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considering. Despite the adoption of an Insider Trading Policy, we may not be able to prevent a director, executive or employee from trading in our common stock on the basis of, or while having access to, material, nonpublic information. If a director, executive or employee was to be investigated, or an action was to be brought against a director, executive or employee for insider trading, it could have a negative impact on our reputation and our stock price. Such a claim, with or without merit, could also result in substantial expenditures of time and money, and divert attention of our management team from other tasks important to the success of our business.

We may encounter difficulties in managing our growth and expanding our operations successfully.

As we seek to advance our product candidates through clinical trials, we will need to expand our development, regulatory, manufacturing, marketing and sales capabilities or contract with third parties to provide these capabilities for us. As our operations expand, we expect that we will need to manage additional relationships with various strategic partners, suppliers and other third parties. Future growth will impose significant added responsibilities on members of management. Our future financial performance and our ability to commercialize our product candidates and to compete effectively will depend, in part, on our ability to manage any future growth effectively. To that end, we must be able to manage our development efforts and clinical trials effectively and hire, train and integrate additional management, administrative and sales and marketing personnel. We may not be able to accomplish these tasks, and our failure to accomplish any of them could prevent us from successfully growing our company.

If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of our product candidates.

We face an inherent risk of product liability as a result of the clinical testing of our product candidates and will face an even greater risk if we commercialize any products. For example, we may be sued if any product we develop allegedly causes injury or is found to be otherwise unsuitable during product testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability, and a breach of warranties. Claims could also be asserted under state consumer protection acts. If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit commercialization of our product candidates. Even successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in:

decreased demand for our product candidates or products that we may develop;

injury to our reputation;

withdrawal of clinical trial participants;

costs to defend the related litigation;

diversion of management's time and our resources;

substantial monetary awards to trial participants or patients;

product recalls, withdrawals or labeling, marketing or promotional restrictions;

loss of revenue;

the inability to commercialize our product candidates; and

a decline in our stock price.

Our inability to obtain and retain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the commercialization of products we develop. We currently carry product liability insurance covering our clinical studies in the amount of \$10 million in the aggregate. Although we maintain such insurance, any claim that may be brought against us could result in a court

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judgment or settlement in an amount that is not covered, in whole or in part, by our insurance or that is in excess of the limits of our insurance coverage. Our insurance policies also have various exclusions, and we may be subject to a product liability claim for which we have no coverage. We will have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts.

We may incur significant costs complying with environmental laws and regulations, and failure to comply with these laws and regulations could expose us to significant liabilities.

We use hazardous chemicals and radioactive and biological materials in certain aspects of our business and are subject to a variety of federal, state and local laws and regulations governing the use, generation, manufacture, distribution, storage, handling, treatment and disposal of these materials. Although we believe our safety procedures for handling and disposing of these materials and waste products comply with these laws and regulations, we cannot eliminate the risk of accidental injury or contamination from the use, manufacture, distribution, storage, handling, treatment or disposal of hazardous materials. In the event of contamination or injury, or failure to comply with environmental, occupational health and safety and export control laws and regulations, we could be held liable for any resulting damages and any such liability could exceed our assets and resources. We do not maintain insurance for any environmental liability or toxic tort claims that may be asserted against us.

Risks Related to Commercialization of Our Product Candidates

We have limited sales, marketing, reimbursement or distribution experience and we will have to invest significant resources to develop those capabilities.

We have limited sales, marketing, reimbursement or distribution experience. To develop internal sales, reimbursement, distribution and marketing capabilities, we will have to invest significant amounts of financial and management resources, some of which will be committed prior to any confirmation that tivozanib will be approved. For product candidates such as tivozanib, where we will have lead commercialization responsibility in North America under our strategic alliance with Astellas, we could face a number of additional risks in developing our commercial infrastructure, including:

we may not be able to attract and build an effective marketing or sales force;

the cost of establishing a marketing or sales force may not be justifiable in light of the revenues generated by any particular product; and

our direct sales and marketing efforts may not be successful.

Furthermore, we have granted Astellas the rights to commercialize tivozanib in Europe and other areas of the world outside of Asia and, where appropriate, we may elect in the future to utilize strategic partners or contract sales forces to assist in the commercialization of ficlatuzumab, AV-203 and future products, if approved. We may have limited or no control over the sales, marketing and distribution activities of these third parties. Our future revenues may depend heavily on the success of the efforts of these third parties.

Our commercial success depends upon attaining significant market acceptance of our product candidates, if approved, including tivozanib and ficlatuzumab, among physicians, patients, health care payors and, in the cancer market, acceptance by the major operators of cancer clinics.

Even if tivozanib, ficlatuzumab or any other product candidate that we may develop or acquire in the future obtains regulatory approval, the product may not gain market acceptance among physicians, health care payors, patients and the medical community. Market acceptance of any products for which we receive approval depends on a number of factors, including:

the efficacy and safety of the product candidate, as demonstrated in clinical trials;

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the clinical indications for which the drug is approved;

acceptance by physicians, major operators of cancer clinics, health care payors, physician networks and patients of the drug as a safe and effective treatment;

with respect to tivozanib, the results obtained in our phase 3 clinical trial for the treatment of advanced clear cell RCC and the extent to which the results demonstrate that treatment with tivozanib represents a clinically meaningful improvement in care as compared to other available VEGF inhibitors;

the potential and perceived advantages over alternative treatments, including, with respect to tivozanib, advantages over Avastin, Nexavar, Sutent, Votrient or other emerging therapies;

the cost of treatment in relation to alternative treatments;

the availability of adequate reimbursement and pricing by third parties and government authorities;

the continued projected growth of oncology drug markets;

relative convenience and ease of administration;

the prevalence and severity of adverse side effects; and

the effectiveness of our sales and marketing efforts.

If our approved drugs fail to achieve market acceptance, we would not be able to generate significant revenue.

Reimbursement may be limited or unavailable in certain market segments for our product candidates, which could make it difficult for us to sell our products profitably.

Market acceptance and sales of our product candidates will depend significantly on the availability of adequate coverage and reimbursement from third-party payors for any of our product candidates and may be affected by existing and future health care reform measures. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which drugs they will pay for and establish reimbursement levels. Reimbursement by a third-party payor may depend upon a number of factors, including the third-party payor's determination that use of a product is:

a covered benefit under its health plan;

safe, effective and medically necessary;

appropriate for the specific patient;

cost-effective; and

neither experimental nor investigational.

Obtaining coverage and reimbursement approval for a product from a government or other third party payor is a time consuming and costly process that could require us to provide supporting scientific, clinical and cost-effectiveness data for the use of our products to the payor. We may not be able to provide data sufficient to gain acceptance with respect to coverage and reimbursement. We cannot be sure that coverage or adequate reimbursement will be available for any of our product candidates. Also, we cannot be sure that reimbursement amounts will not reduce the demand for, or the price of, our products. If reimbursement is not available or is available only to limited levels, we may not be able to commercialize certain of our products.

In both the United States and certain foreign jurisdictions, there have been a number of legislative and regulatory changes to the health care system that could impact our ability to sell our products profitably. In particular, the Medicare Modernization Act of 2003 revised the payment methodology for many products under Medicare. This has resulted in lower rates of reimbursement. There have been numerous other federal and state initiatives designed to reduce payment for pharmaceuticals.

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As a result of legislative proposals and the trend towards managed health care in the United States, third-party payors are increasingly attempting to contain health care costs by limiting both coverage and the level of reimbursement of new drugs. They may also refuse to provide any coverage of approved products for medical indications other than those for which the FDA has granted market approvals. As a result, significant uncertainty exists as to whether and how much third-party payors will reimburse patients for their use of newly approved drugs, which in turn will put pressure on the pricing of drugs. We expect to experience pricing pressures in connection with the sale of any products we may develop or commercialize due to the trend toward managed health care, the increasing influence of health maintenance organizations, additional legislative proposals, as well as country, regional, or local healthcare budget limitations. Any products that we may develop or commercialize may not be considered cost-effective, and coverage and reimbursement may not be available or sufficient to allow us to sell our products on a profitable basis.

Foreign governments may impose price controls, which may adversely affect our future profitability.

We and our strategic partners intend to seek approval to market our future products in both the United States and in foreign jurisdictions. If approval is obtained in one or more foreign jurisdictions, we and our strategic partners will be subject to rules and regulations in those jurisdictions relating to our product. In some foreign countries, particularly in countries in the European Union, the pricing of prescription pharmaceuticals and biologics is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product candidate. If reimbursement of our future products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, we may be unable to achieve or sustain profitability.

Healthcare reform measures could hinder or prevent our product candidates' commercial success.

The U.S. government and other governments have shown significant interest in pursuing healthcare reform. Any government-adopted reform measures could adversely impact the pricing of healthcare products and services in the U.S. or internationally and the amount of reimbursement available from governmental agencies or other third party payors. The continuing efforts of the U.S. and foreign governments, insurance companies, managed care organizations and other payors of health care services to contain or reduce health care costs may adversely affect our ability to set prices which we believe are fair for any products we may develop and commercialize, and our ability to generate revenues and achieve and maintain profitability.

New laws, regulations and judicial decisions, or new interpretations of existing laws, regulations and decisions, that relate to healthcare availability, methods of delivery or payment for products and services, or sales, marketing or pricing, may limit our potential revenue, and we may need to revise our research and development programs. The pricing and reimbursement environment may change in the future and become more challenging due to several reasons, including policies advanced by the U.S. government, new healthcare legislation or fiscal challenges faced by government health administration authorities. Specifically, in both the U.S. and some foreign jurisdictions, there have been a number of legislative and regulatory proposals and initiatives to change the health care system in ways that could affect our ability to sell any products we may develop and commercialize profitably. Some of these proposed and implemented reforms could result in reduced reimbursement rates for our potential products, which would adversely affect our business strategy, operations and financial results. For example, in March 2010, President Obama signed into law a legislative overhaul of the U.S. healthcare system, known as the Patient Protection and Affordable Care Act of 2010, as amended by the Healthcare and Education Affordability Reconciliation Act of 2010, or the PPACA, which may have far reaching consequences for life science companies like us. As a result of this new legislation, substantial changes could be made to the current system for paying for healthcare in the United States, including changes made in order to extend medical benefits to those who currently lack insurance coverage. Extending coverage to a large population could substantially change the structure of the health insurance system and the methodology for reimbursing medical services, drugs and devices. These structural changes could entail modifications to the existing system of private payors and government programs, such as Medicare and Medicaid, creation of a

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government-sponsored healthcare insurance source, or some combination of both, as well as other changes. Restructuring the coverage of medical care in the United States could impact the reimbursement for prescribed drugs, biopharmaceuticals, medical devices, or our product candidates. If reimbursement for our approved product candidates, if any, is substantially less than we expect in the future, or rebate obligations associated with them are substantially increased, our business could be materially and adversely impacted.

Further federal and state proposals and health care reforms could limit the prices that can be charged for the product candidates that we develop and may further limit our commercial opportunity. Our results of operations could be materially adversely affected by the PPACA, by Medicare prescription drug coverage legislation, by the possible effect of such current or future legislation on amounts that private insurers will pay and by other health care reforms that may be enacted or adopted in the future.

Risks Related to Our Dependence on Third Parties

If any of our current strategic partners fails to perform its obligations or terminates its agreement with us, the development and commercialization of the product candidates under such agreement could be delayed or terminated and our business could be substantially harmed.

We currently have strategic partnerships in place relating to certain of our product candidates and technologies as follows:

We recently entered into a strategic partnership with Astellas in connection with which we and Astellas have agreed to develop and commercialize tivozanib in North America and Europe and have exclusively licensed to Astellas rights to develop and commercialize tivozanib in the rest of the world other than Asia.

We have entered into a strategic partnership with OSI, primarily focused on the identification and validation of genes and targets involved in the processes of epithelial-mesenchymal transition or mesenchymal-epithelial transition in cancer.

We have entered into an exclusive option and license agreement with Biogen Idec regarding the development and commercialization of our ErbB3-targeted antibodies for the potential treatment and diagnosis of cancer and other diseases outside of the United States, Canada and Mexico.

These strategic partnerships may not be scientifically or commercially successful due to a number of important factors, including the following:

Each of our strategic partners has significant discretion in determining the efforts and resources that it will apply to their strategic partnership with us. The timing and amount of any cash payments, related royalties and milestones that we may receive under such strategic partnerships will depend on, among other things, the efforts, allocation of resources and successful development and commercialization of our product candidates by our strategic partners under their respective agreements. For instance, under our collaboration with Astellas, we must agree on all development and commercialization plans and strategies for North America and Europe before initiating such activities. If we cannot agree with Astellas with respect to specific development or commercialization initiatives, the program may be delayed or unsuccessful.

Our strategic partners may change the focus of their development and commercialization efforts or pursue higher-priority programs.

Our strategic partners may, under specified circumstances, terminate their strategic partnership with us on short notice and for circumstances outside of our control, which could make it difficult for us to attract new strategic partners or adversely affect how we are perceived in the scientific and financial communities. For example, Merck terminated its collaboration agreement with us related to ficlatuzumab effective December 27, 2010, at which point we assumed responsibility for funding and

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performance of all research and clinical development manufacturing and future commercialization of ficlatuzumab. Astellas can terminate its agreement with us after February 2013 with six months notice and can terminate the entire agreement with us in connection with a material breach of the agreement by us that remains uncured for a specified cure period. OSI can terminate its agreement with us, with respect to any or all collaboration targets and all associated products, upon written notice to us and can terminate the entire agreement with us in connection with a material breach of the agreement by us that remains uncured for a specified cure period. Biogen Idec may not elect to exercise its option to develop and commercialize products relating to our ErbB3 program and, after exercise of its option, may terminate its agreement with us for convenience with respect to any product(s) by providing us with three months prior written notice, or due to a material breach of the agreement by us that is not cured within a short time period or if all of our assets are acquired by, or we merge with, another entity, and the other entity is independently developing or commercializing a product containing an ErbB3 antibody and fails to divest the ErbB3 product within a specified time period.

Our strategic partnership agreements with OSI and Biogen permit our strategic partners wide discretion in deciding which product candidates to advance through the clinical trial process. For example, under our strategic partnership with OSI, it is possible for the strategic partner to reject product candidates at any point in the research, development and clinical trial process, without triggering a termination of the strategic partnership agreement. In the event of any such decision, our business and prospects may be adversely affected due to our inability to progress such candidates ourselves.

OSI or Biogen may develop and commercialize, either alone or with others, products that are similar to or competitive with the product candidates that are the subject of their strategic partnerships with us.

Our strategic partners may enter into one or more transactions with third parties, including a merger, consolidation, reorganization, sale of a substantial amount of its assets, sale of