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)

x **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.

(Exact Name of Registrant as Specified in Its Charter)

Delaware	**04-3581650**
(State or Other Jurisdiction of Incorporation or Organization)	**(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	**Name of each exchange on which registered**
Common Stock, $.001 par value	**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 x

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 x

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 x 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 x (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 x

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 a 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. Ficlatuzumab (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 ficlatuzumab 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 ficlatuzumab. 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 ficlatuzumab.

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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 Sates 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 ³25% 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 ³25% 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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Table 1: Treatment Emergent Related Adverse Events Occurring in >5% of Patients

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.