AVEO PHARMACEUTICALS INC
Form 10-K
March 15, 2016

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, 2015

Or

o 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.)

One Broadway, 14th Floor

Cambridge, Massachusetts 02142

(Address of Principal Executive Offices) (zip code)

Registrant's telephone number, including area code: (617) 588-1960

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 Select 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 o 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 o 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 o

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 x No o

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. o

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	o	Accelerated filer	x
Non-accelerated filer	o (Do not check if a smaller reporting company)	Smaller reporting company	o

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes o 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 Select Market at the close of business on June 30, 2015, was $93,586,098.

The number of shares outstanding of the registrant's Common Stock as of March 9, 2016: 58,181,715.

Documents incorporated by reference:

Portions of our definitive proxy statement for our 2016 annual meeting of stockholders are incorporated by reference into Part III of this Annual Report on Form 10-K.

AVEO PHARMACEUTICALS, INC.

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References to AVEO

Throughout this Form 10-K, the words “we,” “us,” “our” and “AVEO”, except where the context requires otherwise, refer to AVEO Pharmaceuticals, Inc. and its consolidated subsidiaries, and “our board of directors” refers to the board of directors of AVEO Pharmaceuticals, Inc.

Forward-Looking Information

This report contains forward-looking statements regarding, among other things, our and our collaborators’ future discovery, development and commercialization efforts, plans, timelines and strategies, our collaborations, our future operating results, future prospects and financial position, our business strategy, and other objectives for our 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 words and terms of similar meaning. Yo 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, preclinical trials and clinical development activities, our dependence on our existing and future strategic partners, our ability to obtain any necessary financing to conduct our planned 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 and other risk factors. Please refer to the section entitled “Risk Factors” in Part I—Item 1A 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 biopharmaceutical company dedicated to advancing a broad portfolio of targeted therapeutics for oncology and other areas of unmet medical need. Our proprietary platform has delivered unique insights into cancer and related diseases. Our strategy is to leverage these biomarker insights and partner resources to advance the development of our clinical pipeline. We are focused on developing our lead candidate tivozanib in North America as a treatment for renal cell carcinoma and other cancers. We have entered into partnerships to fund the further development of three of our four clinical stage assets, including AV-380, ficlatuzumab, and tivozanib in non-oncologic indications worldwide and oncology indications outside North America. We are also seeking a partnership for AV-203, our fourth development program. These programs and partnerships are described as follows:

- Tivozanib: Tivozanib is a potent, selective, long half-life vascular endothelial growth factor ("VEGF") tyrosine kinase inhibitor ("TKI") of VEGF receptors 1, 2 and 3. In 2006, we acquired the exclusive rights to develop and commercialize tivozanib in all countries outside of Asia under a license from Kyowa Hakko Kirin Co., Ltd. (formerly Kirin Brewery Co. Ltd.), or KHK. We have programs to evaluate tivozanib in several tumor types, including renal cell, colorectal and breast cancer. We are evaluating all options for funding the clinical and regulatory advancement of tivozanib in the programs discussed below, including through partnership with one or more third parties.

RCC First Line Phase 3 Trial (TIVO-1): We conducted a global phase 3 clinical trial comparing the efficacy and safety of tivozanib with Nexavar® (sorafenib), an approved therapy, for first-line treatment of renal cell carcinoma, or RCC. The trial met its primary endpoint for progression-free survival, or PFS, but showed a non-statistically significant trend favoring the sorafenib arm in overall survival, or OS. In June 2013, the U.S. Food and Drug Administration, or FDA, issued a complete response letter informing us that it would not approve tivozanib for the treatment of first line advanced RCC based on the study data from this trial, and recommended that we perform an additional study adequately sized to assure the FDA that there is no adverse effect on OS.

In January 2015, we announced our receipt of confirmation from the European Medicines Agency, or EMA, that tivozanib is eligible for submission of an application for a European Union Marketing Authorization under the Agency's centralized procedure for the treatment of RCC. Confirmation of eligibility for submission is not predictive of the EMA's approval of a Marketing Authorization Application, or MAA. Tivozanib has previously been granted orphan drug designation in Europe for the treatment of RCC. Our partner, EUSA Pharma (UK) Limited, or EUSA, submitted a MAA for tivozanib for the treatment of RCC to the EMA in February 2016 based on our existing dataset, which includes the results from the TIVO-1 study of tivozanib in the first-line treatment of RCC.

TIVO-1 Extension Study (One-way Crossover from Sorafenib to Tivozanib): We have completed a TIVO-1 extension study, known as Study 902, in which patients with advanced RCC received tivozanib as second-line treatment subsequent to disease progression on the sorafenib arm in the TIVO-1 first-line RCC trial. We presented the final results at the 2015 American Society of Clinical Oncology (ASCO) Annual Meeting on June 1, 2015. The final results show a median PFS of 11.0 months and median OS of 21.6 months, demonstrating the clinically meaningful efficacy of tivozanib in a VEGF treatment refractory population. We believe that the long OS derived from tivozanib following sorafenib in Study 902 contributed to the discordance in the results between the PFS benefit which significantly favored tivozanib and the OS which trended in favor of sorafenib in the TIVO-1 trial.

RCC Third Line Phase 3 Trial (TIVO-3): We are planning to conduct a phase 3 trial of tivozanib in the third-line treatment of patients with refractory RCC. The study will use PFS as the primary endpoint and OS as a secondary endpoint to support a request for regulatory approval of tivozanib as a third-line treatment and to address the overall survival concerns from TIVO-1 as a first-line treatment presented in the June 2013 complete response letter from the FDA. Our study design, which we have shared with the FDA, contemplates a randomized, controlled, multi-center, open-label phase 3 study of approximately 322 subjects randomized 1:1 to receive either tivozanib or sorafenib. Subjects enrolled in the study may include those who have received prior immunotherapy, including immune checkpoint (PD-1) inhibitors, reflecting a potentially evolving treatment landscape. The primary objective of the study would be to show improved PFS. Secondary endpoints would include OS and objective response rate, or ORR, as well as safety and pharmacokinetic endpoints.

RCC PD-1 Combination Trial: We are designing a phase 1 study of tivozanib combined with a PD-1 inhibitor for the treatment of patients with RCC. We are evaluating all options for funding, including partnerships, for the clinical and regulatory advancement of tivozanib in combination with PD-1 inhibitors in RCC.

CRC Phase 2 Results: In March 2015, we announced results from a predefined biomarker analysis of our BATON-CRC study, a randomized phase 2 clinical trial of modified FOLFOX6, a commonly used chemotherapy, combined with tivozanib or Avastin® (bevacizumab), which both target angiogenesis signaling pathways, in first line treatment of metastatic CRC. In this study, among prospectively defined biomarkers, patients with low (below the median,

representing 50% of the population) serum neuropilin-1, or NRP-1, a cell surface protein that modulates blood vessel development, showed an improved PFS versus patients with high serum NRP-1 in both treatment arms, supporting the value of serum NRP-1 as a potential prognostic marker for angiogenesis inhibitors. Further, in the subgroup with samples available at the interim analysis, patients identified using a research-use assay to have low serum NRP-1 demonstrated longer PFS when treated with tivozanib compared to bevacizumab, which suggests that first line colorectal cancer patients with low NRP-1 levels may benefit from treatment with tivozanib over bevacizumab, a standard of care in this disease. In April 2015, we presented the results from the phase 2 BATON-CRC study and the Company's ongoing assay development efforts to the FDA in connection with our evaluation of a proposed pivotal phase 3 trial of tivozanib in CRC. In response to questions we posed to the FDA regarding this proposed trial, the FDA suggested that we continue work on the development of our biomarker assay to address variability between assays presented. As such, we hope to identify a commercially viable assay, which may enable a prospectively defined, randomized Phase 2 or Phase 3 study.

Tivozanib Partnerships:

EUSA License Agreement: In December 2015, we entered into a license agreement with EUSA under which we granted EUSA the right to develop and commercialize tivozanib for all diseases and conditions in humans, excluding non-oncologic diseases or conditions of the eye, in Europe (excluding Russia, Ukraine and the Commonwealth of Independent States), Latin America (excluding Mexico), Africa, Australasia and New Zealand. EUSA submitted a MAA for tivozanib for the treatment of RCC with the EMA in February 2016.

Pharmstandard License Agreement: In August 2015, we entered into a license agreement under which we granted to a subsidiary of Pharmstandard OJSC, or Pharmstandard, the exclusive right to develop, manufacture and commercialize tivozanib in the territories of Russia, Ukraine and the Commonwealth of Independent States, or CIS, for all conditions excluding non-oncologic ocular conditions. Under this agreement, Pharmstandard is responsible for all activities and costs associated with the further development, regulatory filings, health services and commercialization of tivozanib in the specified territories. In December 2015, Pharmstandard submitted an application for marketing authorization for tivozanib based on TIVO-1 results in Russia that was accepted by the Ministry of Health in February 2016.

Ophthotech Option for Ocular Conditions (Non-Oncologic): In November 2014, we entered into a research and exclusive option agreement with Ophthotech Corporation, or Ophthotech, under which we granted Ophthotech an option to develop and commercialize tivozanib outside of Asia for the potential diagnosis, prevention and treatment of non-oncologic diseases or conditions of the eye in humans.

- Ficlatuzumab: Ficlatuzumab is a potent Hepatocyte Growth Factor, or HGF, inhibitory antibody. HGF is the sole known ligand of the c-Met receptor which is believed to trigger many activities that are involved in cancer development and metastasis. We have completed two phase 1 clinical studies of ficlatuzumab administered as a single agent and in combination with erlotinib, a TKI, of the epidermal growth factor receptor, or EGFR, and a phase 2 clinical study evaluating ficlatuzumab in combination with gefitinib, an EGFR TKI, in first line non-small cell lung cancer, or NSCLC. The phase 2 trial failed to demonstrate a statistically significant benefit in the intent-to-treat population. However, an exploratory analysis using a serum-based proteomic diagnostic test, known as VeriStrat®, identified a sub-population of patients who experienced a progression free survival and overall survival benefit from the addition of ficlatuzumab to gefitinib. VeriStrat is commercially available to help physicians guide treatment decisions for patients with second line advanced NSCLC. Data from the exploratory analyses with VeriStrat prompted the development of a separate investigational companion diagnostic test called BDX004. Based upon the exploratory analyses, BDX004 may be indicative of a predictive biomarker for the combination of ficlatuzumab and EGFR TKI over EGFR TKI alone in the first line EGFR mutation patients who have been previously identified to not respond well to the current standard of care.

In April 2014, we entered into a worldwide agreement with Biodesix, Inc., or Biodesix, to develop and commercialize ficlatuzumab with BDX004, a serum based diagnostic test which has been derived from the VeriStrat test, employing the same methodology and data processing algorithms as VeriStrat, for use in a confirmatory clinical trial. Pursuant to

the Biodesix agreement, in December 2014 we initiated a phase 2 confirmatory study of ficlatuzumab, which we refer to as the FOCAL study, in combination with erlotinib in first line advanced NSCLC patients who have an EGFR mutation and who are identified by the BDX004 test as being most likely to benefit from the addition of ficlatuzumab to the EGFR TKI. We began enrolling patients during the second half of 2015. Biodesix will fund up to $15 million of the cost of this study, as well as all of the costs associated with development and registration of BDX004, and any additional development, regulatory and commercial costs for ficlatuzumab will be shared equally. Under the Biodesix agreement, subject to regulatory approval, AVEO would lead worldwide commercialization of ficlatuzumab.

- AV-203: AV-203 is a potent anti-ErbB3 (also known as HER3) specific monoclonal antibody with high ErbB3 affinity. We have observed potent anti-tumor activity in mouse models. AV-203 selectively inhibits the activity of the ErbB3 receptor, and our preclinical studies suggest that neuregulin-1, or NRG1 (also known as heregulin), levels predict AV-203 anti-tumor activity in preclinical models. We have completed a phase 1 dose escalation study of AV-203, which

established a recommended phase 2 dose of AV-203 at 20mg/kg intravenously every 2 weeks, demonstrated good tolerability and promising early signs of activity, and reached the maximum planned dose of AV-203 monotherapy. No anti-drug antibodies were detected, and pharmacokinetic results indicated a dose-proportional increase in levels of AV-203.

The expansion cohort of this study among patients with a specific biomarker has been discontinued. We are seeking to pursue further clinical development of AV-203 with a strategic partner.

- AV-380: AV-380 is a potent humanized IgG1 inhibitory monoclonal antibody targeting growth differentiating factor-15, or GDF15, a divergent member of the TGF-ß family, for the potential treatment or prevention of cachexia. Cachexia is defined as a multi-factorial syndrome of involuntary weight loss characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment. Cachexia is associated with various cancers as well as diseases outside of cancer including chronic kidney disease, congestive heart failure, and chronic obstructive pulmonary disease, or COPD. We believe that AV-380 represents a unique approach to treating cachexia because it addresses key underlying mechanisms of the syndrome and focuses on a significant area of patient need. It is estimated that approximately 30% of all cancer patients die due to cachexia and over half of cancer patients who die do so with cachexia present. (J Cachexia Sarcopenia Muscle 2010). In the United States alone, the estimated prevalence of cancer cachexia is over 400,000 patients, and the prevalence of cachexia due to cancer, COPD, congestive heart failure, frailty and end stage renal disease combined is estimated to total more than 5 million patients (Am J Clin Nutr 2006).

In September 2014, we presented the results from four preclinical studies of AV-380 in various in vivo cachexia models and in vitro assays at the 2nd Cancer Cachexia Conference held in Montreal Canada. Our research was also selected for presentation in an oral session at the conference. In April 2015, we also presented the results from a preclinical study of AV-380 in a cachectic human tumor xenograft model at the Annual Meeting of the American Association of Cancer Research. We have established preclinical proof of concept for GDF15 as a key driver of cachexia by demonstrating, in animal models, that the administration of GDF15 induces cachexia, and that inhibition of GDF15 reverses cachexia and provides a potential indication of an overall survival benefit.

In August 2015, we entered into a license agreement under which we granted Novartis International Pharmaceutical Ltd., or Novartis, the exclusive right to develop and commercialize AV-380 and related AVEO antibodies. Under this agreement, Novartis is responsible for all activities and costs associated with the further development, regulatory filing and commercialization of AV-380 worldwide.

In connection with the AV-380 program, we have in-licensed certain patents and patent applications from St. Vincent's Hospital in Sydney, Australia. We have demonstrated preclinical proof-of-concept for AV-380 in multiple cancer cachexia models and have completed cell line development.

Product Pipeline

We were founded with the goal of developing a fundamentally new kind of pre-clinical 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 utilized these novel models to identify and validate target genes that drive tumor growth, to identify drugs that can block the function of these targets, and to identify patients who are most likely to respond favorably to treatment with such drugs. Our cancer models, together with the various techniques we developed to use these models to aid in the discovery and development of new cancer drugs, were used to develop our product pipeline and are collectively referred to as our Human Response Platform.

Tivozanib: Inhibitor of VEGF Receptors 1, 2 & 3

Tivozanib is a potent, selective long half-life inhibitor of all three VEGF receptors that is designed to optimize VEGF blockade while minimizing off-target toxicities. The demonstrated clinical results for tivozanib are supported by its

core biochemical properties of potency, selectivity and long half-life inhibition of all three VEGF receptors. The potency of tivozanib across VEGF receptors 1, 2 and 3 provides a comprehensive blockade of the VEGF pathway. Its high level of selectivity for all three VEGF receptors is designed to minimize unintended side effects, such as fatigue, diarrhea and hand-foot syndrome, which are often associated with the currently approved therapies. Hypertension and dysphonia were the most commonly reported side effects in patients treated with tivozanib.

In 2012, we announced detailed data from our global, phase 3 clinical trial comparing the efficacy and safety of tivozanib with Nexavar® (sorafenib), an approved therapy, for first-line treatment of RCC. This phase 3 trial met its primary endpoint PFS but showed a non-statistically significant trend favoring the sorafenib arm in overall survival. Based on a review of our application for approval of the use of tivozanib for the treatment of first line advanced RCC, in June 2013, the U.S. Food and Drug Administration issued a complete response letter informing us that they would not approve tivozanib at this time based on these study data.

In August 2014, our collaboration and license agreement with Astellas terminated, at which time all rights for the development and commercialization of tivozanib reverted to AVEO. We had entered into the collaboration and license agreement with Astellas in February 2011, pursuant to which we and Astellas shared responsibility for tivozanib, including expenses for continued development and any future commercialization of tivozanib, in North America and Europe. Upon reversion back to AVEO of rights previously granted to Astellas, we reevaluated our tivozanib regulatory and development strategy, as well as partnering opportunities.

In January 2015, we announced our receipt of confirmation from the European Medicine Agency that tivozanib is eligible for submission of an application for a European Union Marketing Authorization under the Agency's centralized procedure for the treatment of RCC. Confirmation of eligibility for submission is not predictive of the European Medicines Agency's approval of a Marketing Authorization Application. Tivozanib has previously been granted orphan drug designation in Europe for the treatment of RCC. In December 2015, we entered into a license agreement with EUSA, under which we granted EUSA the right to develop and commercialize tivozanib for all diseases and conditions in humans, excluding non-oncologic diseases or conditions of the eye, in Europe (excluding Russia, Ukraine and the Commonwealth of Independent States), Latin America (excluding Mexico), Africa, Australasia and New Zealand. EUSA submitted a MAA for tivozanib for the treatment of RCC with the EMA in February 2016.

In August 2015, we entered into a license agreement under which we granted Pharmstandard the exclusive right to develop, manufacture and commercialize tivozanib in the territories of Russia, Ukraine and the Commonwealth of Independent States, or CIS, for all conditions excluding non-oncologic ocular conditions. Under this agreement, Pharmstandard is responsible for all activities and costs associated with the further development, regulatory filings, health services and commercialization of tivozanib in the specified territories. In December 2015, Pharmstandard submitted an application for marketing authorization for tivozanib based on TIVO-1 results in Russia that was accepted by the Ministry of Health in February 2016.

We also have evaluated tivozanib in additional clinical programs including our BATON (Biomarker Assessment of Tivozanib in ONcology) program, assessing biomarkers in solid tumors that may be predictive of clinical response to tivozanib in patients with metastatic colorectal cancer, and other clinical trials assessing locally recurrent or metastatic triple negative breast cancer.

The BATON-BC study in patients with breast cancer, led by AVEO, initiated patient enrollment in December 2012 in a randomized, double-blind, multi-center phase 2 clinical trial, evaluating the efficacy of tivozanib in combination with paclitaxel compared to placebo in combination with paclitaxel in patients with locally recurrent or metastatic triple negative breast cancer who have received no more than one systemic therapy for advanced or metastatic breast cancer. On January 30, 2014, we announced that we and Astellas jointly decided to discontinue the BATON-BC clinical trial, due to insufficient enrollment.

The BATON-CRC study, led by Astellas, which enrolled a total of 265 patients randomized 2 to 1, was an open-label, phase 2 study with a primary endpoint evaluating the superiority of tivozanib in combination with modified FOLFOX6, a standard chemotherapy, compared to bevacizumab in combination with modified FOLFOX6 as first-line treatment in patients with advanced metastatic colorectal cancer. On December 13, 2013, we announced that the study was unlikely to meet the primary endpoint in the intent-to-treat population and on February 14, 2014, we announced that we and Astellas agreed to discontinue this study. The data from the preplanned interim analysis of this study was presented at the European Society for Medical Oncology, or ESMO, on September 29, 2014. The final data through February 28, 2014, including predefined biomarker data from the study, were presented at the American Association for Cancer Research, or AACR Tumor Angiogenesis and Vascular Normalization Conference in March 2015.

An objective of the BATON-CRC study was the assessment of prospectively defined biomarkers that may be predictive of response in selected patient subpopulations. Among these, patients with low (below the median, representing 50% of the patient population) neuropilin-1, or NRP-1, showed an improved PFS versus patients with

high NRP-1 in both treatment arms, supporting the value of NRP-1 as a potential prognostic marker for angiogenesis inhibitors. Further, patients with low serum NRP-1 demonstrated longer PFS when treated with tivozanib (17.9 months, n=52), compared to bevacizumab (11.2 months, n=28) (HR=0.380, p=0.0075). Patients with high NRP-1 had inferior PFS outcomes regardless of treatment assignment, with progression free survival of 7.3 months and 7.5 months for the tivozanib and bevacizumab arms, respectively. As soluble NRP-1 is known to bind to VEGF and is believed to inhibit VEGF binding to VEGF Receptor 2, we hypothesize that VEGF inhibitors may only be effective in patients with low serum NRP-1 levels, and that in patients with low serum NRP-1, a more complete blockade of VEGF pathway inhibition may be beneficial. Of note, exploratory biomarker analyses from two prior studies with tivozanib in RCC presented at the 17th Annual Symposium on Anti-Angiogenesis and Immune Therapies in February 2015 indicated that NRP-1 is a possible biomarker of tivozanib efficacy in patients with RCC. We hope to identify a commercially viable assay, which may enable a prospectively defined, randomized Phase 2 or Phase 3 study.

We are planning to conduct a phase 3 trial of tivozanib in the third-line treatment of patients with refractory RCC. The study will use PFS as the primary endpoint and OS as a secondary endpoint to support a request for regulatory approval of tivozanib as a third-line treatment and to address the overall survival concerns from TIVO-1 as a first line treatment presented in the June 2013 complete response letter from the FDA. Our study design, which we have shared with the FDA, contemplates a randomized, controlled, multi-center, open-

label phase 3 study of approximately 322 subjects randomized 1:1 to receive either tivozanib or sorafenib. Subjects enrolled in the study may include those who have received prior immunotherapy, including immune checkpoint (PD-1) inhibitors, reflecting a potentially evolving treatment landscape. The primary objective of the study would be to show improved PFS. Secondary endpoints would include OS and objective response rate, or ORR, as well as safety and pharmacokinetic endpoints. We are evaluating all options for funding, including partnerships, for the clinical and regulatory advancement of tivozanib in RCC as well as colorectal cancer, or CRC.

In November 2014, we entered into a Research and Exclusive Option Agreement with Ophthotech Corporation, pursuant to which we provided Ophthotech an exclusive option to enter into a definitive license agreement under which we would grant Ophthotech the right to develop and commercialize tivozanib outside of Asia for the potential diagnosis, prevention and treatment of non-oncologic diseases or conditions of the eye in humans. Pursuant to this option agreement, we granted to Ophthotech an exclusive, royalty free license or sublicense, as applicable, under our intellectual property rights solely to perform the research and development activities related to the use of tivozanib as set forth in the development plan during the option period described below. These activities include formulation work for ocular administration, preclinical research and the conduct of a phase 1/2a, proof of concept clinical trial of a product containing tivozanib in patients with wet age-related macular degeneration. Ophthotech may exercise its option at any time until the latest to occur of: (i) twelve (12) months after the achievement of a certain clinical efficacy milestones, (ii) ninety (90) days after the date Ophthotech is required to make certain clinical efficacy milestone payments, and (iii) thirty (30) days after AVEO and Ophthotech agree as to the definitive form of license agreement.

Ficlatuzumab: Hepatocyte Growth Factor (HGF) Inhibitory Antibody

Through the use of our Human Response Platform, our scientists 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, which is 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, head and neck, gastric, bladder, breast, ovarian, prostate and colorectal cancers, certain sarcomas and in multiple myeloma and leukemias. There are no approved therapies that selectively target the HGF/c-Met pathway.

In September 2014, at the 2014 Congress of the European Society for Medical Oncology, or ESMO, we presented the results of our exploratory analysis using a serum-based molecular diagnostic test to identify a patient sub-population that experienced a progression free survival and overall survival benefit on the combination therapy in the ficlatuzumab phase 2 trial. The results suggest that VeriStrat, a serum protein test that is commercially available to help physicians guide treatment decisions for patients with NSCLC, may be selective of positive clinical response for ficlatuzumab plus gefitinib over gefitinib alone. For this retrospective exploratory analysis, 180 pre-treatment serum samples analyzed with VeriStrat and were assigned a label of either “VeriStrat Good” (VSG) or “VeriStrat Poor” (VSP) (VSG=145, VSP=35). While the study failed to demonstrate improved OS or PFS over gefitinib alone in the intent-to-treat population, the addition of ficlatu