Initiation
**Overweight**

**AVEO, AVEO US**
Price: $9.39

**Price Target: $14.00**

# AVEO Pharmaceuticals, Inc.

## Unpartnered and Differentiated in Oncology; Initiating at Overweight

We are initiating coverage of AVEO Pharmaceuticals with an Overweight rating and a $14 price target. AVEO is a pure-play oncology company whose key value driver is tivozanib, an oral cancer drug in phase 3 trials for renal cell carcinoma (RCC). We think tivozanib has $1B peak potential globally in RCC. Importantly, it has a validated mechanism of action (VEGF inhibition), which is a leading indictor of success in other VEGF-sensitive tumor types. Indeed, AVEO is conducting phase 1b trials of tivozanib in breast and colon cancer as well as NSCLC which in aggregate could be a $2B+ opportunity with supporting data. Opportunities outside of RCC are free call options, in our view, and they are not included in our AVEO model. Within RCC, the market is crowded but our physician checks indicate enthusiasm for tivozanib's phase 2 data with differentiation seen in the data. With phase 3 data in RCC coming in 2H11 but likely signals of clinical activity in many other tumor types in 2010, we think that visibility of tivozanib should continue to increase in the near term.

- **We think tivozanib is largely de-risked in RCC.** AVEO's phase 2 trial of tivozanib yielded 11.8-month PFS (progression-free survival) in 272 RCC patients, which favorably compared to two market-leading agents: Onyx's Nexavar (5.5 months) and Pfizer's Sutent (11.0 months). Perhaps more impressive is tivozanib's favorable tolerability profile with only 3.7% of patients requiring a dose interruption, very few grade 4 adverse events, and a low rate of SAEs overall. Hence, with an ongoing phase 3 trial in RCC that is a head-to-head study against Nexavar, we are quite comfortable with the likelihood of technical success, and we think that tivozanib could emerge as a best-in-class drug for RCC.
- **Partnership a potential catalyst.** We have assumed an EU partnership in our AVEO model in 2011 but with relatively conservative terms. We think this is necessary to maximize value for tivozanib in the longer term from a clinical development and commercial perspective. That said, the scarcity value of unpartnered phase 3 cancer drugs is very high with robust M&A activity for oncology companies with partnered drugs.
- **Tivozanib, AV-299, and AV-203 all offer shots on goal.** Future tivozanib expansion in breast, colon, and lung cancer as well as liver and brain cancer all are reasonable given the MOA. AVEO's pipeline includes AV-299 (partnered with Merck) starting phase 2 trials in NSCLC and AV-203 (partnered with Biogen) in preclinical for solid tumors, which offer additional shots on goal.
- **Valuation attractive.** Our price target is $14 (49% upside) based on 5X 2013E revenues (second year of tivozanib sales in RCC), discounted to today at a 25% rate.

**US Biotechnology**

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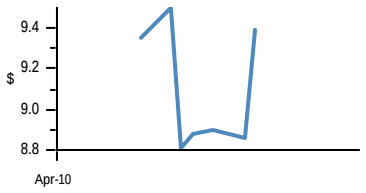
**Price Performance**




| | YTD | 1m | 3m | 12m |
|---|---|---|---|---|
| Abs | 0.4% | 0.4% | 0.4% | 0.4% |

**AVEO Pharmaceuticals, Inc. (AVEO;AVEO US)**

| | 2008A | 2009E | 2010E | 2011E | 2012E |
|---|---|---|---|---|---|
| EPS Reported ($) | | | | | |
| Q1 (Mar) | | | (0.85) | | |
| Q2 (Jun) | | | (0.63) | | |
| Q3 (Sep) | | | (0.71) | | |
| Q4 (Dec) | | | (0.72) | | |
| FY | (0.46) | (2.03) | (2.91) | (1.76) | (2.15) |

Source: Company data, Bloomberg, J.P. Morgan estimates.

| Company Data | |
|---|---|
| Price ($) | 9.39 |
| Date Of Price | 20 Apr 10 |
| 52-week Range ($) | 9.61 - 8.16 |
| Mkt Cap ($ mn) | 291.09 |
| Fiscal Year End | Dec |
| Shares O/S (mn) | 31 |
| Price Target ($) | 14.00 |
| Price Target End Date | 31 Dec 10 |

See page 26 for analyst certification and important disclosures, including non-US analyst disclosures.

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# Key Investment Points

## AVEO Pharmaceuticals (AVEO)

**Overweight**

**Initiating coverage of AVEO with an Overweight rating and a $14 price target**
AVEO is a pure-play, small-cap oncology company in phase 3 development. The company's key value driver is tivozanib, an oral cancer drug in phase 3 trials for renal cell carcinoma (RCC). The RCC market is crowded in the US and EU, but we think that tivozanib is differentiated and has the potential to be a best-in-class drug. Our model implies peak potential for tivozanib of $1B globally with only 30-35% share of the US and EU RCC markets. Indeed, our calls with oncologists on the clinical profile of tivozanib suggest a robust commercial profile that couples strong efficacy (best PFS among its competitors) and a very favorable toxicity profile (best AE profile overall). If phase 3 data in 2H 2011 are as strong as those seen in phase 2 trials, we think that tivozanib could quickly become a standard of care in RCC.

**Call option on other tivozanib indications**
Importantly, tivozanib has a well-validated and broad mechanism of action (VEGF inhibition), which is a leading indictor of success in other VEGF-sensitive tumor types. To this end, AVEO is conducting phase 1b trials of tivozanib in breast and colon cancer as well as NSCLC, with more indications such as liver and brain cancer likely to be studied. Given the long duration of IP protection (composition of matter expiry in 2022 with Hatch-Waxman extension potentially to 2027), AVEO is well positioned to leverage robust activity in RCC into many other tumor types. Our model formally accounts for sales in RCC only. With phase 3 data in RCC coming in 2H11, but likely signals of clinical activity in many other tumor types in 2010, we think that visibility and profile of tivozanib in the oncology community should increase.

**RCC clinical data is differentiated**
AVEO's phase 2 trial of tivozanib yielded an 11.8-month PFS in 272 RCC patients, which favorably compared to the PFS seen with two market leaders: Onyx's Nexavar (5.5 months) and Pfizer's Sutent (11.0 months). Among patients with clear-cell RCC (most common type) and prior nephrectomy, the median PFS was calculated at 14.8 months and these are the specific patients being studied in the ongoing phase 3 trial in RCC (called TIVO-1). Also impressive is tivozanib's favorable tolerability profile with only 3.7% of patients requiring a dose interruption, very few grade 4 adverse events, and a low rate of SAEs overall. Hence, we are comfortable that tivozanib could beat Nexavar in TIVO-1 by at least 3 months on PFS and we're comfortable with a PFS that could match that of Sutent (11 months).

**Partnership terms could be robust**
AVEO has been able to develop tivozanib into phase 3 without a partner which is very rare for a drug that could become a best-in-class agent. Hence, AVEO has significant scarcity value with considerable M&A activity seen with many biotech companies that have already partnered their key asset (e.g., OSI Pharma, Millennium, ImClone, Pharmion, MGI Pharma, etc.). We have assumed an OUS partnership in our model in 2011 but with conservative economics ($100M upfront/25% royalties but no R&D funding and no milestones).

**Platform and pipeline offer several shots on goal**
AVEO's pipeline includes AV-299 (partnered with Merck) which is starting phase 2 trials in NSCLC and AV-203 (partnered with Biogen) in preclinical for solid tumors. AVEO's platform technology – called Human Response Platform – is productive and has attracted technology partnerships with companies such as OSI Pharma.

# Investment Risks

**Clinical risk**
Late-stage clinical trials are very difficult to predict, and it could be difficult for tivozanib to show similar data in the ongoing phase 3 trial that is similar to its phase 2 study. Meeting the three-month PFS benefit over Nexavar to achieve the TIVO-1 primary endpoint is critical to AVEO shares, and it is a key source of clinical risk and a risk to our Overweight rating.

**Commercial risk**
AVEO has not developed a commercial team and the RCC market is quite competitive with more than six players in the space, including major pharmas with deep pockets. Hence, even with differentiated data for tivozanib, AVEO may not be able to compete effectively in the US market (assuming the company retains all US rights); also AVEO's EU partner may not be able to compete (assuming the company partners in this region).

**Regulatory risk**
In the event of successful clinical programs for tivozanib in RCC, AVEO would then face regulatory risk for approval. If FDA does not accept PFS as a primary endpoint and a surrogate for overall survival, tivozanib may face major difficulties garnering approval from FDA or EMEA.

**Financing risk**
Following completion of its initial public offering and assuming cash burn of around $35M the last two quarters, AVEO should have ~$108M in cash on hand as of March 31, 2010, enough to complete the current phase 3 development of tivozanib in RCC without economics from a partnership. We forecast additional burn of around $60M in 2010, with additional financings occurring in 2011 and 2012. That said, the company may still need to raise capital above what we anticipate in the public markets, further diluting current shareholders in order to bring additional indications forward for tivozanib.

**Legal risk**
Inability to defend tivozanib patents in the US or Europe could substantially limit the commercial opportunity. AVEO holds composition of matter patents that typically defend intellectual property in the US and Europe expiring in 2022, with the US patents being eligible for Hatch-Waxman extension to 2027.

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## Company Description

Based in Cambridge, MA, AVEO Pharmaceuticals is a development-stage biotech company focused on the discovery and development of novel oncology therapeutics. AVEO completed its initial public offering on March 18, 2010. The company's key value-driving asset is tivozanib, currently in a phase 3 trial called the TIVO-1 study for renal cell carcinoma (RCC; a.k.a. kidney cancer). Tivozanib is an orally available and specific inhibitor of the vascular endothelial growth factor (VEGF) receptor with applications in many other tumor types such as NSCLC, breast cancer, and colorectal cancer. Tivozanib is being tested in these other indications and potentially many others such as liver and brain cancer. In addition to tivozanib, AVEO's pipeline includes AV-299, a HGF (hepatocyte growth factor) inhibitor in co-development with Merck for solid tumors, with NSCLC being the initial indication. AVEO's platform technology known as its "Human Response Platform" is an efficient engine for oncology drug discovery and has yielded candidates including AV-203 (partnered with Biogen).

## Background

AVEO completed its initial public offering in March 2010, raising almost $81M including exercise of the over-allotment option. Following initial phase 1 data for tivozanib in 2007 which demonstrated encouraging activity in RCC, AVEO has been focused on advancing this indication and now is in a phase 3 registration trial for RCC (called TIVO-1). The company is also evaluating tivozanib in phase 1b trials in multiple other tumor types including breast and colon cancer as well as NSCLC. In addition, AVEO has diversified the pipeline behind tivozanib with two candidates, AV-299 and AV-203, both for oncology indications. Prior to its IPO, AVEO had raised $169M from strategic partners including Merck, Biogen Idec, OSI Pharmaceuticals, and Schering Plough (now Merck). Following its IPO and assuming cash burn of around $35M in 4Q09 and 1Q10, AVEO's estimated cash/short-term investments total about $108M, which should be sufficient through 2011, when the phase 3 TIVO-1 trial yields data.

## Clinical Pipeline

AVEO is focusing on the development of tivozanib in multiple tumor types with renal cell carcinoma being the lead indication. The company successfully completed a phase 2 study for tivozanib in 272 patients with advanced RCC, yielding an overall median progression-free survival (PFS) of 11.8 months. Currently, tivozanib is in a 500-patient pivotal phase 3 study (called TIVO-1) in RCC being led by key opinion leader Dr. Robert Motzer from the Memorial Sloan-Kettering Cancer Center. We anticipate completion of enrollment by YE 2010, with data in 4Q11 and an NDA filing in 1H 2012 in the US. Looking beyond RCC, tivozanib is also in phase 1b development for metastatic breast cancer, NSCLC, and colorectal cancer, none of which are factored into our AVEO model. Behind tivozanib, AVEO is developing AV-299 (in collaboration with Merck), a HGF inhibitor (antibody) that is entering a phase 2 study in NSCLC and several phase 1 studies in advanced solid tumors and multiple myeloma. Additionally, AVEO also has a pre-clinical candidate, AV-203 (antibody), which is being targeted for phase 1 development in the near term under collaboration with Biogen.

Table 1: AVEO Pipeline Overview

| Product | Indication | Pre-clinical | Ph I | Ph II | Ph III | NDA | Marketed |
|---|---|---|---|---|---|---|---|
| Tivozanib monotherapy | RCC | | | | | | |
| Tivozanib + Torisel | RCC | | | | | | |
| Tivozanib monotherapy | NSCLC | | | | | | |
| Tivozanib + paclitaxel | mBC | | | | | | |
| Tivozanib + FOLFOX6 | CRC | | | | | | |
| AV-299 + Iressa | NSCLC | | | | | | |
| AV-299 | Solid tumor, MM | | | | | | |
| AV-299 | Advanced solid tumor with liver mets | | | | | | |
| AV-203 | Solid tumors | | | | | | |

Source: Company reports.

## Catalysts and Milestones

AVEO has several value-driving catalysts in 2010, with additional follow-up phase 2 data in RCC expected at the 2010 ASCO meeting (June 4-8; Chicago). Tivozanib phase 1b data in multiple cancer indications, including CRC, NSCLC, and mBC, are also expected in 2010, either at ASCO or the ESMO Congress (October 8-12; Milan). In 2011, the key event will be the data from phase 3 study TIVO-1 of tivozanib in RCC. We expect this data to form the basis of an NDA filing in early 2012 and potential FDA approval by YE12 (see Table 2 for details). We are also assuming economics from an OUS partnership in our model in 2011.

Table 2: AVEO Pharmaceuticals – Clinical Catalysts and Expected Events

| Est. Timing | Drug | Indication | Event | Significance |
|---|---|---|---|---|
| Jun 4 -8, 2010 | Tivozanib | RCC | Detailed Phase 2 data at ASCO | Medium |
| 2010 | Tivozanib | mBC | Phase 1b data | Medium |
| 2010 | Tivozanib | CRC | Phase 1b data | Medium |
| 1H 2010 | AV-299 | NSCLC | Initiate Phase 2 combination trial | Low |
| 2010 | Tivozanib | NSCLC | Phase 1b data | Medium |
| 3Q10 | AV-299 | MM | Phase 1 data | Medium |
| 2010 | Tivozanib | RCC | Phase 1 data – Torisel combo study | Medium |
| 2011 | Tivozanib | All | Sign OUS Partnership | High |
| 1H 2011 | Tivozanib | RCC | Initiate trial for competitive differentiation | Low |
| 4Q 2011 | Tivozanib | RCC | TIVO-1 data | High |
| 1H 2012 | Tivozanib | RCC | FDA Filing | Medium |
| 1H 2012 | Tivozanib | RCC | EMEA Filing | Medium |
| YE 2012 | Tivozanib | RCC | FDA approval | High |
| 2013 | Tivozanib | RCC | EMEA approval | High |

Source: Company data and J.P. Morgan estimates.

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# Tivozanib in RCC – The Lead Indication

AVEO's key value driver is tivozanib, a potent, once-daily, orally available compound in phase 3 development for RCC. Its mechanism of action is a selective inhibitor of vascular endothelial growth factor (VEGR) receptors 1, 2, and 3. Tivozanib has clear potential to be a best-in-class agent in RCC, in our view. The phase 3 RCC trial, called TIVO-1, is currently enrolling patients with data likely maturing by YE 2011. Given its broad and validated mechanism, tivozanib is also in early stages of clinical development for NSCLC, breast, and colorectal cancer. AVEO owns exclusive global rights for all indications of tivozanib excluding Asia, where partner Kyowa Hakko Kirin has retained rights. From an IP perspective, AVEO holds composition of matter protection in the US and EU until 2022, before potential Hatch-Waxman extension in the US until 2027.

## Renal Cell Carcinoma – Background

RCC is a type of cancer that originates in the proximal renal tubular epithelium. Prior to the recent evolution of the RCC treatment paradigm with many targeted therapies approved, immunomodulating therapies (interferon alpha and interleukin-2) were widely used despite a modest benefit and substantial toxicity. Today, there are six specifically targeted agents approved for RCC (see Table 3 below), though the risk/ benefit profile still could be improved given substantial toxicity associated with these agents.

*Epidemiology*

RCC is the third most common genitourinary cancer in the US based on American Cancer Society estimates. Indeed, there were 57,760 new cases of renal cell carcinoma (kidney and renal pelvis) with 12,980 deaths in the last year[1]. Although the historical growth rate of RCC incidence was ~2% per year, recent estimates reveal a 6% increase in incidence over the last year.

Overall, five-year survival rates for RCC are about 68%[2]. As seen in Table 3 below, tumors that are confined to the kidney or have spread to nearby tissues have yielded five-year survival rates of ~96% and ~64%, respectively. For those with distant metastases, or those that have spread beyond Gerota's fascia, the five-year survival can be as low as 23%. There are very few early warning signs/symptoms for RCC, and as a result about one third of patients present with metastatic disease at the time of diagnosis. Indeed, up to 40% of those who are treated for localized disease eventually develop metastases[3].

Table 3: RCC Staging and 5-Year Survival Rates

| Stage | Description | 5-Yr Survival |
|---|---|---|
| I | Tumor is 7cm or less and limited to the kidney | 96% |
| II | Tumor is more than 7cm and limited to the kidney | 82% |
| III | Tumor has invaded in a single regional lymph node and major veins but not beyond Gerota's fascia | 64% |
| IV | Tumor has distant metastasis or involvement of adjacent organs | 23% |

Source: Adapted from the National Comprehensive Cancer Network (NCCN) and National Cancer Institute.

[1] http://www.cancer.org/downloads/STT/500809web.pdf.
[2] http://seer.cancer.gov/statfacts/html/kidrp.html.
[3] Lam J. *et al. World J Urol; 23: 202-212* (2005).

*Pathophysiology*

There are five major subtypes of RCC based on histology/cell type and growth characteristics: clear-cell, chromophilic, chromophobic, oncocytic, and collecting-duct tumors (see Table 4). Clear-cell carcinoma is the predominant RCC cell type (75-85% of tumors), with many of the recently approved agents in RCC targeting this subtype. Obesity, smoking, and hypertension are included as some of the risk factors associated with the development of spontaneous RCC. There are several hereditary forms of RCC such as von Hippel-Lindau disease caused by inactivating mutations of the VHL tumor suppressor gene and papillary renal cancer (type 1), associated with mutations in the c-Met oncogene.

Table 4: Pathological Classification of RCC

| Type | Growth pattern | Cell of origin | Incidence (%) |
|---|---|---|---|
| Clear-cell | Acinar or sarcomatoid | Proximal tubule | 75–85 |
| Chromophilic | Papillary or sarcomatoid | Proximal tubule | 12–14 |
| Chromophobic | Solid, tubular, or sarcomatoid | Intercalated cell of cortical collecting duct | 4–6 |
| Oncocytic | Typified by tumor nests | Intercalated cell of cortical collecting duct | 2–4 |
| Collecting-duct | Papillary or sarcomatoid | Medullary collecting duct | 1 |

Source: *N Engl J Med; 335:865-75 (1996)*.

## Pathogenesis

Advances in both basic and clinical research have uncovered two major signaling pathways utilized in advanced RCC. These include the vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) pathways (see Figure 1). Both of these pathways are thought to mediate tumor angiogenesis, which is a key process for sustaining growth of the underlying tumor.

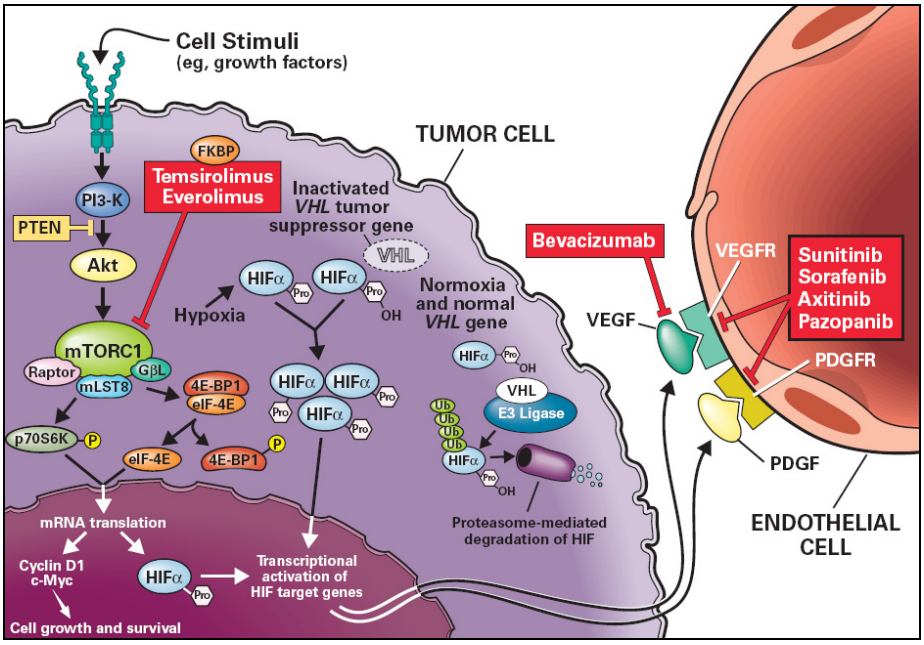
The VEGF and mTOR pathways are up-regulated by various factors in a cancer state, such as hypoxia, cytokines, and inactivation of tumor-suppressor genes such as *VHL* (von Hippel- Lindau)[4]. *VHL* regulates hypoxia-inducible factor-1 (HIF), a transcription factor that controls the cellular response to low oxygen, which also induces the expression of VEGF. Under normal conditions, *VHL* encodes VHL protein which targets HIF for cellular degradation using the ubiquitin/proteasome machinery. Under hypoxic conditions or inactivation of *VHL*, HIF is not subjected to degradation which drives its accumulation. This change in signaling equilibrium results in an excess of pro-angiogenic factors including VEGF, as well as an activation of the mTOR pathway. Activated mTOR phosphorylates p70S6K which leads to enhanced transcriptional activity of HIF.

The biopharmaceutical industry has been prolific in RCC – there are currently six approved therapies for advanced RCC, all targeting either of the two main pathways, VEGF or mTOR. Among the agents that target the VEGF pathway are Roche's bevacizumab (a MAb to VEGF) which binds to circulating VEGF ligand, whereas Pfizer's sunitinib, Bayer/Onyx's sorafenib, and GSK's pazopanib inhibit the tyrosine kinase activity of VEGF receptors. The other two, Pfizer's temsirolimus and Novartis' everolimus, are analogues of rapamycin and work through inhibiting the mTOR pathway. We discuss the two classes of agents in greater detail in the next section. Several other anti-VEGF agents are currently under development, including tivozanib, axitinib, and cediranib. Additionally, several clinical trials are also under way to investigate various strategies to integrate VEGF and mTOR targeted therapies

[4] Brian I. Rini. *J Clin Oncol 27:3225-3234* (2009).

(such as tivozanib in combination with temsirolimus, bevacizumab plus temsirolimus).

Figure 1: Plausible Pathways of Renal Cell Carcinoma




Source: *J Clin Oncol 27:3225-3234* (2009).

## The Current Treatment Paradigm

Early stages of renal cancer are asymptomatic and in about 25-35% of cases, RCC is discovered as an incidental finding from an imaging study (e.g., CT scan, MRI, or ultrasound) for another medical condition. The classic triad of flank pain, hematuria, and abdominal mass is uncommon (10%) and is generally indicative of advanced disease[5]. In a few cases, patients complain of symptoms resulting from metastatic disease, like bone pain, adenopathy, etc.

*Surgery Remains Standard of Care in Non-Metastatic Disease*
For Stage I-III RCC, surgical resection, either simple or radical, remains the cornerstone of treatment. According to NCCN, about 20-30% of patients relapse after surgery with a median time to relapse of about 1-2 years and few of them receive systemic therapy. Systemic therapy may include both immunotherapy (IL-2 or IFN-a), and more recently targeted therapies that inhibit pathways known to be involved in the pathogenesis of renal cell cancer.

*Options Available for Metastatic Disease*
Nephrectomy may benefit selected Stage IV RCC patients, depending upon the primary RCC treatment, solitary site of metastasis, and individual patient considerations. In fact, in the era of immunotherapy (when no targeted therapies were available) there was a strong recommendation of nephrectomy upfront, but now with expanded treatment options, the vast majority of patients receive targeted therapy.

[5] Motzer R. *et al, N Engl J Med; 335:865-75 (1996)*.

**Cytokine Therapies**

Historically, cytokine-based immunotherapy using interferon-a (IFN-a) and IL-2 were the mainstay for the treatment of metastatic RCC. However, the response rates to these therapies have been modest and inconsistent and sometimes occur at the expense of great cost and toxicity and hence are rarely used these days. In terms of activity, high-dose IL-2 has a higher objective response rate of approximately 20%, compared with low-dose cytokines (13%), with durable responses in only a small percentage (5% to 7%) of patients.[6] [7] [8] Furthermore, high-dose therapy is associated with high toxicity, notably hypotension, myocardial infarction, CNS orientation, malaise, and elevated bilirubin levels. For IFN-a therapy, previous studies suggest that some patients may benefit from initial nephrectomy followed by administration of interferon-alpha. When used in conjunction with surgery, IFN-a yields OS of 17 months compared to 7 months in patients receiving interferon-alpha alone (HR = 0.54, $P = 0.03$)[9]. But despite the survival benefit in the IFN-a + surgery arm, there were no differences in response rates between the two groups. This is not surprising given the poor correlation between response rates and survival in RCC.

**Targeted Therapies**

There are six molecularly targeted agents available for the treatment of RCC. In Table 5 below, we compare the efficacy-safety profile of these targeted agents. These novel agents targeting angiogenesis pathway appear promising and have expanded the treatment options in RCC. With almost all of these targeted agents exhibiting "class side effects," the important consideration in choosing a therapy is meaningful extension of progression-free survival or the overall survival of a given patient.

Table 5: Comparative Efficacy/Safety Profile of Targeted Agents in Phase 3 Trials in Renal Cell Carcinoma

| | | | | | Clinical benefit | | | |
|---|---|---|---|---|---|---|---|---|
| Agent | Mechanism | Setting | Comparator | No. of patients | PFS (months) | OS (months) | Primary end point, Met | Adverse effects |
| Nexavar (sorafenib) | VEGFR and other kinase inhibitor | Advanced RCC, clear cell, Cytokine refractory | Placebo | 903 | 5.5 v 2.8 (HR = 0.44) | 19.3 v 15.9 (HR = 0.77) | OS: no | Hypertension, diarrhea, rash, hand-foot syndrome, dyspnea |
| Sutent (sunitinib) | VEGFR and other kinase inhibitor | 1st line, clear cell | IFN | 750 | 11 v 5 (HR = 0.42) | 26.4 v 21.8 (HR = 0.82) | PFS: yes | Neutropenia, thrombocytopenia, hypertension, diarrhea, hand-foot syndrome |
| Avastin (bevacizumab) | VEGF ligand binding antibody | 1st line, clear cell | IFN | 649 | 10.2 v 5.5 (HR = 0.57) | 23.3 v 21.3 (HR = 0.86) | OS: no | Fatigue, asthenia, proteinuria, neutropenia, hypertension. |
| Votrient (pazopanib) | VEGFR and other kinase inhibitor | 1st line, clear cell | Placebo | 435 | 9.2 v 4.2 (HR = 0.46) | Not mature | PFS: yes | Diarrhea, hypertension, hair color change, nausea, fatigue, anorexia, vomiting |
| Torisel (temsirolimus) | mTOR inhibitor | 1st line, poor risk group only | IFN | 626 | 5.5 v 3.1 (HR = 0.66) | 10.9 v 7.3 (HR = 0.73) (p=0.008) | OS: yes | Asthenia, edema, pain, mucositis, rash. |
| Afinitor (everolimus) | mTOR inhibitor | 2nd line who failed VEGF TKI | Placebo | 416 | 4.9 v 1.9 (HR = 0.33) | Not mature | PFS: yes | Stomatitis, rash, fatigue, diarrhea, anorexia, nausea, mucosal inflammation |

Source: J.P. Morgan Research.

[6] Fyfe G. *et al, J Clin Oncol; 13:688-696* (1995).
[7] Yang J. *et al, J Clin Oncol; 21:3127-3132* (2003).
[8] Klapper J. *et al, Cancer; 113(2):293-301* (2008).
[9] Mickisch G. *et al, Lancet*; *358: 966-70* (2001).

**Nexavar**

Nexavar (sorafenib; Bayer and Onyx Pharmaceuticals) was the first approved targeted therapy available for advanced RCC patients. In pivotal phase 3 trials, Nexavar has shown a prolonged PFS benefit compared with placebo in cytokine-refractory patients. The median PFS was 5.5 months in the Nexavar group and 2.8 months in the placebo group (HR= 0.44; 95% CI 0.35–0.55)[10]. Although the overall response rate was modest compared with other available agents, it was higher than placebo (10% vs. 2%). The median overall survival was 19.3 months for patients in the Nexavar group and 15.9 months for patients in the placebo group (HR= 0.77), but the benefit was statistically insignificant. For the first-line treatment, Nexavar failed to show a PFS benefit over IFNa (5.7 vs. 5.6 months), although Nexavar-treated patients had greater tumor shrinkage (68% vs. 39%)[11]. Hence, it is largely used as second-line therapy for metastatic RCC. Common AEs for Nexavar were diarrhea, rash, hand-foot syndrome, dyspnea, and hypertension.

**Sutent**

A month after Nexavar was approved, Sutent (sunitinib; Pfizer) received FDA approval for advanced renal cell cancer in January 2006. Sutent has shown clinical benefit in both cytokine-refractory (ORR and DR) and treatment-naïve patients (PFS and ORR). In a randomized phase 3 study, first-line treatment of Sutent resulted in significant improvements in PFS (11 vs. 5 months, HR=0.42) and ORR (47% vs. 12%; p<0.001) compared to IFN.[12] [13] The median overall survival of patients treated with Sutent was longer (26.4 vs. 21.8 months), but the increase was not significant (p=0.05). The most common side effects include neutropenia, thrombocytopenia, hypertension, diarrhea, and hand-foot syndrome.

**Avastin**

Avastin (bevacizumab; Roche/Genentech) was FDA approved for advanced renal cancer in combination with IFN-α in August 2009. In the phase 3 AVOREN study, the addition of Avastin to IFN significantly increased PFS (10.2 vs. 5.5 months; HR=0.57) and ORR (31% vs. 12%). Updated results demonstrate a median OS of 23.3 months in the Avastin + IFN arm and 21.3 months in the IFN + placebo arm (HR 0.86).[14] [15] Like the previous trials of Nexavar and Sutent, OS failed to reach statistical significance here as well. The most commonly reported grade 3 or worse adverse events were fatigue, asthenia, proteinuria, neutropenia, and hypertension.

**Votrient**

Votrient (pazopanib; GSK) received FDA approval in October 2009 for patients with advanced renal cell carcinoma. The phase 3 study evaluated both treatment-naïve and patients with one prior cytokine-based systemic therapy. In terms of activity, Votrient significantly prolonged PFS compared with placebo in the overall ITT study population (9.2 vs. 4.2 months; HR=0.46) as well as the treatment-naive subpopulation (11.1 vs. 2.8 months; HR=0.40) and the cytokine-pretreated subpopulation (7.4 vs. 4.2 months; HR=0.54)[16]. The objective response rate looked in line with Avastin and in fact, better than Nexavar (30% vs. 3%). The most common

[10] Escudier B. *et al, N Engl J Me; 356:125-34* (2007).
[11] Escudier B. *et al, J Clin Oncol; 27:1280-1289* (2009).
[12] Motzer R. *et al, N Engl J Med; 356:115-24* (2007).
[13] Motzer R. *et al, J Clin Oncol; 27: 3584-3590* (2009).
[14] Escudier B. *et al, J Clin Oncol 27:15s, 2009 (suppl; abstr 5020).*
[15] Escudier B. *et al, Lancet*; 370: 2103-11 (2007).
[16] Sternberg C. *et al, J Clin Oncol; 28:1061-1068* (2010).

side effects include diarrhea, hypertension, hair color change, nausea, fatigue, anorexia, and vomiting. Importantly, Votrient was associated with severe and fatal hepatotoxicity as indicated by elevated level of ALT and AST in phase 3 studies and hence a need to monitor hepatic function regularly during treatment.

**Torisel**

Torisel (temsirolimus; Pfizer) is the first mTOR inhibitor which received FDA approval in advanced RCC in June 2007. It is the only approved agent that has shown statistically significant improvement in overall survival compared with IFN (10.9 vs. 7.3 months; HR=0.73; p=0.008)[17]. Torisel arm also showed significantly better PFS as compared to IFN arm (5.5 vs. 3.1 months; HR=0.66). Of note, the phase 3 trial evaluated Torisel as 1L treatment in patients with poor prognostic features only. In terms of safety, our talks with physicians suggest that Torisel has the cleanest profile among all other available agents. The notable common AEs are asthenia, edema, pain, mucositis, and rash.

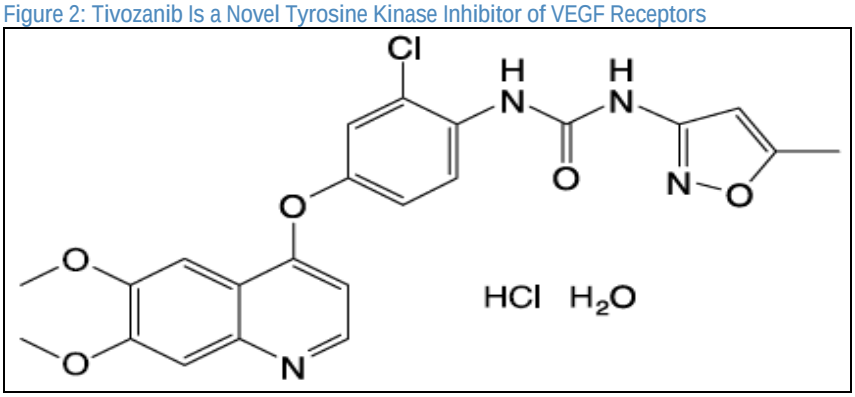
**Afinitor**

Afinitor (everolimus; Novartis) was approved for the treatment of patients with advanced RCC after failure of treatment with Sutent or Nexavar in March 2009. It is the first and the only agent that has shown clinical benefit in patients who have progressed on other targeted therapies. Afinitor significantly prolongs progression-free survival relative to placebo (4.9 vs. 1.9 months; HR=0.33; p<0.001)[18]. The objective tumor response rates were minimal at 2% and 0% for Afinitor and placebo, respectively. Common adverse reactions with Afinitor include stomatitis, rash, fatigue, diarrhea, anorexia, nausea, mucosal inflammation, vomiting, and cough.

# Tivozanib – MOA and Clinical Data

Tivozanib (or AV-951 or KRN951, N-{2-Chloro-4-[(6,7-dimethoxy-4-quinolyl)oxy]phenyl}-N-(5-methyl-3-isoxazolyl) urea hydrochloride monohydrate) is a novel oral quinoline-urea derivative, which is a highly potent and selective inhibitor of vascular endothelial growth factor (VEGF) receptors 1, 2, and 3.

Figure 2: Tivozanib Is a Novel Tyrosine Kinase Inhibitor of VEGF Receptors




Source: *Cancer Res;* 66: 18, 9134-9142 (2006).

[17] Torisel PI.
[18] Afinitor PI.

## Mechanism of Action

Tivozanib potently inhibits the tyrosine kinase activity of all three VEGF receptors: VEGFR-1, 2, and 3 with subnanomolar IC50 values (IC50 = 0.21, 0.16, and 0.24 nmol/L, respectively)[19]. The receptor tyrosine kinase plays a major role in stimulating tumor angiogenesis and metastatic cancer progression. It also inhibits ligand-induced phosphorylation of platelet-derived growth factor receptor-B (PDGFR-B) and c-Kit (IC50 = 1.72 and 1.63 nmol/L, respectively).

Preclinical studies suggest that tivozanib blocks the VEGF-mediated proliferation and migration of endothelial cells in vitro. Additionally, *in vivo* studies demonstrate tivozanib's antitumor activity against a broad spectrum of human tumor xenografts, including lung, breast, colon, ovarian, pancreas, and prostate cancer. Tivozanib is differentiated from other tyrosine kinase inhibitors in 1) it is significantly more potent in-vitro activity in VEGF-dependent proliferation of human endothelial cells (IC50=0.67 nmol/L) as compare to 4 nmol/L for Sutent[20], and 2) it has shown highly selective and strong in-vivo activity with a wide variety of antitumor activities at very low doses (0.2 or 1 mg/kg/d).

## Tivozanib Clinical Data Overview

AVEO is conducting several trials for tivozanib in multiple cancer indications (renal cell carcinoma, mBC, NSCLC, CRC, and other gastrointestinal tumors). The key completed, ongoing, and planned trials are listed in Table 6. Tivozanib in RCC is by far the lead value driver for AVEO with positive dataset in hand for phase 2 studies. The WW phase 3 trial in advanced RCC is currently enrolling and data is anticipated by YE11. In addition, the company plans to conduct a phase 3 extension study to assess the long-term safety profile of tivozanib.

Table 6: Tivozanib Clinical Development

| Trial | N | Setting | Phase | General Design | Geography | Status |
|---|---|---|---|---|---|---|
| AV-951-103 | 30 | CRC, gastrointestinal cancer | Ph 1 | Open-label, dose-escalation study of tivozanib + FOLFOX6 | Netherlands | Enrolling |
| AV-951-07-102 | 27 | RCC | Ph 1b | Open-label, dose-finding study of tivozanib in combination with Torisel in RCC | US | Enrolling |
| AV-951-08-104 | 84 | mBC | Ph 1b/2a | Non-Randomized, open-label study of tivozanib in combination with paclitaxel | US, Germany | Enrolling |
| AV-951-08-105 | 53 | NSCLC | Ph 1b/2a | Non-Randomized, open-label, dose finding study of tivozanib | US | Enrolling |
| AV-951-07-201 | 272 | RCC | Ph 2 | Randomized, open-label, pbo cont study for 16 wks: Pbo/1.5 mg QD | Russia, India | Completed |
| TIVO-1 | 500 | RCC | Ph 3 | Randomized, open-label study to compare tivozanib (1.5 mg QD) to sorafenib (400mg BID) (1:1) | Global | Enrolling |
| TIVO-1 extension study | 500 | RCC | Ph 3 ext study | Randomized, open-label study to compare tivozanib (1.5 mg QD) to sorafenib (400mg BID) (1:1) | US | Enrolling |

Source: Company reports, clinicaltrials.gov, and J.P. Morgan estimates.

## Early Clinical Data

In January 2007, AVEO licensed worldwide rights (excluding Asia) to tivozanib (previously called KRN951) from Kirin Brewery Co., Ltd., a research-driven company based in Tokyo, Japan. The first signal of tivozanib activity was observed

[19] Nakamura K. *et al.* Cancer Res; 66: 18, 9134-9142 (2006).
[20] Mendel D. *et al. Clinical* Cancer Res; 9: 327-337 (2003).

in a phase 1 study in 41 patients with advanced solid tumors. The takeaway from this trial was that tivozanib was well tolerated with hypertension being the most commonly observed toxicity, which is an expected mechanism-based side effect of VEGF inhibitors. In terms of activity, 9 of the 41 patients had refractory RCC and all of them showed either partial response or stable disease (2PR, 7SD). Interestingly, tivozanib yielded modest responses (SD) in multiple tumor types including colorectal, lung, and pancreatic acinar cell carcinoma. Notably, 33% of patients across all tumor types achieved tumor shrinkage. Study results also indicated tivozanib's maximum tolerated dose of 1.5 mg/day given for four consecutive weeks followed by a two-week rest period. These results look promising and tivozanib's high potency allows it to be administered at doses much lower than other approved targeted therapies.

## Phase 2 Review

As a follow-up to phase 1 data, AVEO initiated a 272-patient phase 2 study in fall of 2007. This randomized, placebo-controlled, open-label trial enrolled metastatic RCC patients naïve to VEGF-targeted therapies at more than 30 sites in Russia, Ukraine, and India under a US IND filing. In the design, all patients were treated with 1.5 mg/day of tivozanib for 16 weeks (4 cycles of 3 weeks on, 1 week off) at which point they were evaluated for tumor growth and divided into three groups: 1) responders, as defined by a >25% tumor shrinkage, were kept on tivozanib for an additional 12 weeks; 2) patients with SD, or <25% tumor change (shrinkage or growth), were randomized to tivozanib or placebo in a double-blind fashion for 12 weeks; and 3) non-responders, as defined by a >25% increase in tumor growth, discontinued the study. The trial was designed using randomized discontinuation protocol to determine whether SD was related to drug. The baseline characteristics are highlighted in Table 7 below.

Table 7: Tivozanib: Key Phase 2 Baseline Characteristics

| | |
|---|---|
| No. of patients | 272 |
| Age (median years) | 56 |
| Male / Female (%) | 70% / 30% |
| White / Asian (%) | 93% / 7% |
| ECOG Status (0/1) | 49% / 51% |
| Prior Nephrectomy | 73% |
| Clear cell / Non clear cell | 83% / 17% |
| Number of prior treatments | |
| • 0 | 54% |
| • ≥ 1 | 46% |
| MSKCC Prognostic Score | |
| Favorable | 30% |
| Intermediate | 57% |
| Poor | 8% |
| Unknown | 5% |

Source: Company reports.

The primary efficacy endpoints were: (1) objective response rate (ORR) at 16 weeks; (2) percentage of randomly assigned patients remaining progression free at 12 weeks following randomization (i.e., 28 weeks after study start); and (3) safety profile. The key secondary endpoints included overall progression-free survival (PFS) from start of treatment and PFS after random assignment to tivozanib or placebo.

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## Robust Efficacy

The phase 2 data were initially released in February 2009 but were subsequently updated at ASCO 2009. Overall, there were 76 patients that responded and were kept on tivozanib for the full 28-week period (group 1 above), 118 patients with SD (group 2 above), and 21 patients with PD who were discontinued (group 3 above). Importantly, of the 118 patients randomized to tivozanib or placebo, there was a statistically significant percentage of patients on tivozanib who remained progression free at 28 weeks (55% vs. 28%; p=0.004), verifying that tivozanib was indeed active in patients with stable disease.

**Best PFS of Any RCC Agents in Market**

The overall median progression-free survival (PFS) for the entire study population was 11.8 months, as determined by the independent reviewers. Analysis of the prospectively defined subset of 176 patients with clear-cell histology and history of prior nephrectomy (the population being studied in the phase 3 trial) demonstrated a median PFS of 14.8 months. We view the PFS benefit as extremely encouraging, and better than any other agent currently available on the market. Even more impressive (although it was a retrospective analysis) is the fact that patients with clear-cell RCC AND prior nephrectomy had a median PFS of 14.8 months. Importantly, these two factors (clear-cell and prior nephrectomy) are entry criteria for the ongoing TIVO-1 study.

**Impressive Response Rates**

Tivozanib yielded 27% ORR when assessed by independent radiological review (see Table 8 for a summary of key efficacy metrics). The investigator-assessed response was 35%, which suggests to us that the attending physicians saw signs of improvement regardless of the formal response assessment by independent reviewers.

Table 8: Summary of Key Efficacy Metrics in Phase 2 Study

| | |
|---|---|
| Median PFS | 11.8 months |
| ORR | 26.8% |
| DCR | 84.2% |
| % of pts progression free at 12 wks following randomization (investigator assessed) | |
| - tivozanib | 55% |
| - placebo | 28% |
| Median duration of treatment | 8.5 months |
| Median duration of response | Not mature yet |

Source: Company reports.

**Waterfall Plot Supportive of Tivozanib Activity**

Although the central review response rate was 25% by independent radiologists, the waterfall plot of tumor change from baseline is more descriptive of the clinical course of the treated population (see Figure 3). Indeed, it is clear that most patients either had no change or had a robust reduction in tumor burden. The disease control rate (DCR) approached 84%, suggesting that only 16% of patients had progressive disease.

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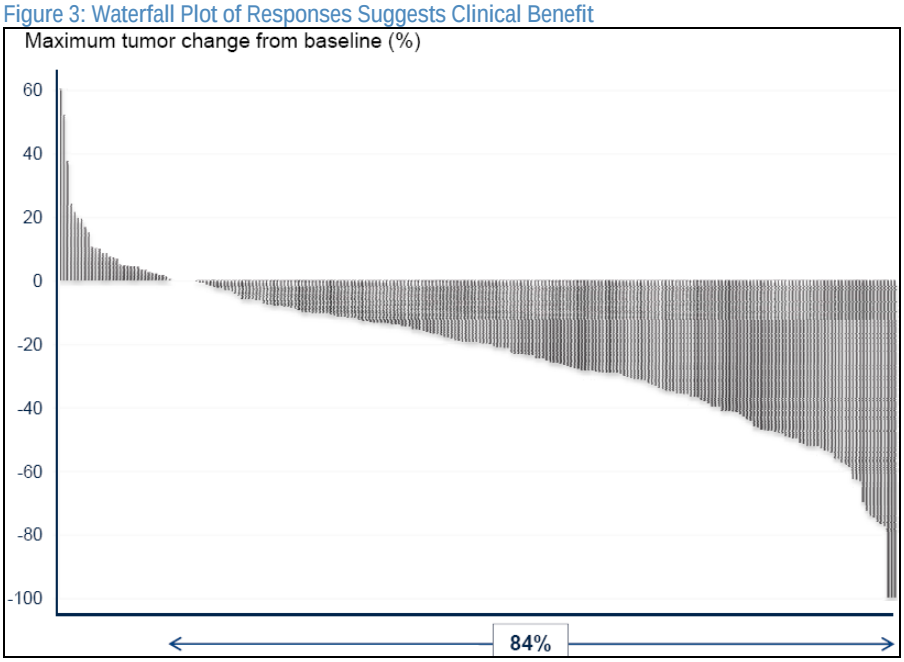
Figure 3: Waterfall Plot of Responses Suggests Clinical Benefit




Source: Company reports.

## Safety Profile Appears Clean

Overall, the safety findings in the randomized phase 2 trial of tivozanib are encouraging, in our view. Hypertension is by far the most common toxicity in patients and can be usually managed using standard anti-hypertensive drugs. Approximately 50% of patients suffered from hypertension with 8.8% of those having grade 3/4 symptoms (see Table 9). The other common side effects are dysphonia (22%), and asthenia (13%), diarrhea (12%), and fatigue (8%). The events that were noticeably less frequent in this tivozanib phase 2 trial compared to those observed with other VEGFR inhibitors were hand-foot syndrome, mucositis/ stomatitis, neutropenia, and proteinuria. Notably, only 10.3% and 3.7% of patients required a dose reduction and interruption, respectively. Overall, we think that tivozanib has favorable safety profile and can be safely combined with other anti-cancer therapies, which could be a key differentiating factor when compared with other targeted therapies.

Table 9: Comparative Safety Profile of Tivozanib and Other Approved/Under Development Targeted Agents in Renal Cell Carcinoma

| | Approved targeted therapies | | | | | Agents under development | | |
|---|---|---|---|---|---|---|---|---|
| Single Agent Toxicity All grades (Gr 3 /4) | Sutent (n=375) | Nexavar (n=451) | Votrient (n=290) | Torisel (n=208) | Afinitor (n=274) | Tivozanib (n=272) | Axitinib (n=52) | Cediranib (n=43) |
| Hypertension | 30% (12%) | 17% (4%) | 40% (4%) | 7% | 2% | 54.4% (8.5%) | 30% (8%) | (30%) |
| Dysphonia | | | | | | 22% (0) | 19% (0) | |
| Mucositis / Stomatitis | 30% (1%) | | | 41% (3%) | 42% (3%) | 4.4% (0) | 9% (1%) | |
| Hand-foot syndrome | 29% (9%) | 30% (6%) | 6% (<1%) | | | 3.0% (0) | | |
| Rash | 24% (1%) | 40% (1%) | 8% (<1%) | 47% (5%) | 28% (1%) | 5.8% (0.7%) | 6% (0%) | |
| Diarrhea | 61% (9%) | 43% (2%) | 52% (3%) | 27% (1%) | 21% (2%) | 12% (0.4%) | 31% (5%) | |
| Fatigue | 54% (11%) | 37% (5%) | 19% (2%) | | 23% (3%) | 8% (1.5%) | 27% (4%) | (26%) |
| Anemia | 79% (8%) | 8% (3%) | | 45% (20%) | 91% (9%) | 15.1% (1.8%) | | |
| Neutropenia | 77% (18%) | | 34% (1%) | 7% (3%) | 11% (0) | 10.0% (2.2%) | | |
| LFT elevation (AST) | 56% (2%) | | 53% (7%) | 38% (2%) | 25% (1%) | 20% (<1%) | | |
| Dose reduction | 50% | 13% | 36% | 23% | 5% | 10.3% | 29% | NA |
| Dose Interruption | 38% | 21% | 42% | 66% | 34% | 3.7% | NA | NA |

Source: J.P. Morgan Research.

## Next Steps – Phase 3 in RCC

AVEO began a pivotal trial (TIVO-1) of tivozanib in advanced RCC in December 2009. In this randomized, open-label, controlled trial, patients will be randomized 1:1 to receive 1.5 mg QD tivozanib or 400 mg BID sorafenib. TIVO-1 is expected to enroll 500 patients in sites across the US, Canada, South America, Europe, and India. Unlike the phase 2 trial, TIVO-1 will enroll only clear-cell RCC patients who have had prior nephrectomy. The primary endpoint of the trial is to compare PFS of tivozanib vs. sorafenib. The trial is 90% powered to detect at least a 3-month PFS improvement over sorafenib. This endpoint was agreed with FDA and EMEA, where the objective is to show improvement. TIVO-1 will include secondary endpoints of OS, ORR, DOR, and safety/tolerability.

**Single-Agent Therapy a Start; New Combinations May Improve Tivozanib Efficacy**

Apart from monotherapy, tivozanib is also being investigated as a combination therapy (with mTOR inhibitor, Torisel) in advanced RCC. The phase 1b, open-label, 36-patient trial is assessing the safety, tolerability, and optimal dosing for the combination. Preliminary data at the last AACR meeting indicated that 1.5 mg QD tivozanib in combination with weekly IV Torisel was well tolerated with no dose-limiting toxicities and there were initial signs of efficacy. The combination showed a high rate of tumor shrinkage in 12 (out of 16) patients with two partial responses. The interim results look impressive, especially when we know that previous combination trials have failed due to severe toxicities. Given the favorable tolerability profile and minimal "off-target" toxicities observed as a single agent in the phase 2 trial, our doc calls with RCC experts indicate that its efficacy is likely to be much more impressive in combination therapy.

## Emerging Competitive Agents in RCC?

There are several targeted agents currently under development in advanced RCC, including Pfizer's axitinib, AstraZeneca's cediranib and zactima, and Amgen's AMG 386. Axitinib and Cediranib (both VEGF inhibitors) are by far the lead agents, followed by others in early-stage development.

Axitanib is the closest compound in clinical studies for RCC behind tivozanib. Pfizer has completed an open-label phase 2 study in 2L RCC and is currently enrolling two phase 3 trials in first- and second-line RCC. If approved, we expect the drug to reach the market at around the same time as tivozanib. Data from a 52-patient phase 2 trial in cytokine-refractory RCC patients showed compelling efficacy, including 44% objective response rate based on RECIST criteria[21]. Median TTP was 15.7 months and median overall survival was 29.9 months. However, we note that these efficacy data are probably slightly inflated, as they were not reviewed by an external review committee. In terms of safety, diarrhea, hypertension, fatigue, and dysphonia are the most common adverse events.

AstraZeneca's cediranib is currently in a phase 2 trial for the first-line treatment of RCC. Interim data was presented at ASCO 2008, and demonstrated an impressive

[21] Rixe O. *et al. Lancet Oncol*; 8: 975-84 (2007).

38% ORR[22]. Median PFS was 8.7 months and most frequent treatment-related AEs included hypertension, fatigue, and joint pain.

### Other Solid-Tumor Indications Potential Longer-Term Drivers

In a phase 1 trial tivozanib demonstrated clinical benefit in multiple advanced solid tumors. As a follow-up to the phase 1 data, the company is conducting clinical trials in several cancer indications including mBC, NSCLC, CRC, and other gastrointestinal tumors. These trials are currently enrolling and are expected to provide data in 2010.

**Breast Cancer**
AVEO is conducting a phase 1b/2a trial of Tivozanib in combination with paclitaxel in patients with advanced or metastatic breast cancer. The trial is a multi-center, open-label trial in 84 evaluable patients that employs a response rate endpoint. Secondary endpoints include duration of response and time to progression. Interim safety data from the trial is expected in 2010.

**Colorectal Cancer**
This is a phase 1b, open-label, dose-finding study evaluating tivozanib in combination with FOLFOX6 in 30 patients with advanced colorectal and other gastrointestinal cancers. Interim safety data from the trial is expected in 2010.

**Non-Small Cell Lung Cancer**
In 2009, AVEO initiated phase 1b/2a tivozanib monotherapy trial to assess safety/tolerability and maximum tolerated dose of tivozanib in NSCLC. The primary endpoint of the trial is to determine ORR and secondary endpoints included duration of response and TTP. Efficacy data is anticipated from the study in 2010.

## Tivozanib Commercial Considerations

We are assuming an NDA filing for tivozanib in RCC in the US in early 2012 with late 2012 approval and launch. In Europe, our model assumes EU approval in 2013 following the early ’12 filing. We assume AVEO will partner in Europe and receives a royalty on EU sales at a rate of roughly 25%. Overall, our peak sales forecast in the US is in 2019 with sales of $513M, and our peak opportunity in the EU is assumed in 2019 with sales of $473M.

**Our US Assumptions**
We conservatively assume 51,190 newly diagnosed RCC patients in the US in 2010, of which around 30% have metastatic disease. For pricing, we model $5,125/month, and assume 2.5% price increases each year. We think tivozanib’s clinical profile will warrant premium pricing over Sutent, Nexavar, or Torisel. In all, we are assuming US product sales of $29M, $151M, and $232M in the first three years of launch (2012-2014), which reflects penetration rates of 3%, 15%, and 22%, respectively.

[22] Sridhar S. *et al. J Clin Oncol* 26: 2008 (May 20 suppl; abstr 5047).

**Our EU Assumptions**

We assume that AVEO will partner tivozanib in the EU and other OUS countries. We assume tivozanib will launch in the EU in 2013 and estimate peak EU sales of $473M in 2019, of which we estimate AVEO will earn a 25% royalty.

Table 10: Tivozanib RCC Revenue Model

| RCC Market Model | 2010E | 2011E | 2012E | 2013E | 2014E | 2015E | 2016E | 2017E | 2018E | 2019E |
|---|---|---|---|---|---|---|---|---|---|---|
| US Tivozanib Sales | $0.0 | $0.0 | $28.7 | $150.6 | $232.1 | $299.2 | $360.9 | $415.9 | $462.7 | $513.1 |
| EU Tivozanib Sales | $0.0 | $0.0 | $0.0 | $70.4 | $197.2 | $259.0 | $299.3 | $357.4 | $420.5 | $473.3 |
| WW Tivozanib Sales | $0.0 | $0.0 | $28.7 | $221.0 | $429.3 | $558.2 | $660.3 | $773.3 | $883.2 | $986.4 |
| | | | | | | | | | | |
| US Renal Cell Carcinoma | | | | | | | | | | |
| Newly RCC Diagnosed Patients (US) | 51,190 | 52,470 | 53,781 | 55,126 | 56,504 | 57,917 | 59,365 | 60,849 | 62,370 | 63,929 |
| % Metastatic Disease + 5% of Stage 3 | 30% | 30% | 30% | 30% | 30% | 30% | 30% | 30% | 30% | 30% |
| Available Patients | 15,357 | 15,741 | 16,134 | 16,538 | 16,951 | 17,375 | 17,809 | 18,255 | 18,711 | 19,179 |
| *Penetration* | *0.0%* | *0.0%* | *3.0%* | *15.0%* | *22.0%* | *27.0%* | *31.0%* | *34.0%* | *36.0%* | *38.0%* |
| Treated Patients | 0 | 0 | 484 | 2,481 | 3,729 | 4,691 | 5,521 | 6,207 | 6,736 | 7,288 |
| Duration of treatment (months) | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 |
| Monthly cost | 5,125 | 5,253 | 5,384 | 5,519 | 5,657 | 5,798 | 5,943 | 6,092 | 6,244 | 6,400 |
| US Tivozanib Sales ($M) | $0.0 | $0.0 | $28.7 | $150.6 | $232.1 | $299.2 | $360.9 | $415.9 | $462.7 | $513.1 |
| | | | | | | | | | | |
| EU Renal Cell Carcinoma | | | | | | | | | | |
| Newly RCC Diagnosed Patients (EU) | 59,816 | 61,311 | 62,844 | 64,415 | 66,025 | 67,676 | 69,368 | 71,102 | 72,879 | 74,701 |
| % Metastatic Disease + 5% of Stage 3 | 30% | 30% | 30% | 30% | 30% | 30% | 30% | 30% | 30% | 30% |
| Available Patients | 17,945 | 18,393 | 18,853 | 19,324 | 19,808 | 20,303 | 20,810 | 21,331 | 21,864 | 22,410 |
| *Penetration* | *0.0%* | *0.0%* | *0.0%* | *6.0%* | *16.0%* | *20.0%* | *22.0%* | *25.0%* | *28.0%* | *30.0%* |
| Treated Patients | 0 | 0 | 0 | 1,159 | 3,169 | 4,061 | 4,578 | 5,333 | 6,122 | 6,723 |
| Duration of treatment (months) | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 |
| Monthly cost | 5,125 | 5,253 | 5,384 | 5,519 | 5,657 | 5,798 | 5,943 | 6,092 | 6,244 | 6,400 |
| EU Tivozanib Sales ($M) | $0.0 | $0.0 | $0.0 | $70.4 | $197.2 | $259.0 | $299.3 | $357.4 | $420.5 | $473.3 |

Source: J.P. Morgan estimates.

# Antibody Platform

Beyond tivozanib, AVEO also has a proprietary antibody development platform that has produced two key candidates: AV-299, which is partnered with Merck and is entering phase 2 studies in non-small cell lung cancer (NSCLC), and AV-203, which is partnered with Biogen and is in preclinical for solid tumors.

## AV-299

AV-299 is a highly potent monoclonal antibody targeting the hepatocyte growth factor (HGF). This is a novel target in oncology, but it has broad implications in a variety of solid tumors including lung cancer, breast cancer, pancreatic cancer, and malignant glioma. It has been shown to be additive to Tarceva and Erbitux *in vivo* in lung cancer models, and there is potential that it could be used with other anticancer agents as well. AV-299 is being studied in combination with Iressa in a fairly large phase 2 study in 188 Asian patients with first-line NSCLC who will be randomized

to AV-299 + Iressa vs. Iressa alone. It is possible that initial data could be available in 2011, but more likely 2012. Additionally, AV-299 is also being studied in patients with advanced solid tumors or multiple myeloma, as well as in patients with advanced solid tumors that also have liver met.

AVEO is developing AV-299 in collaboration with Merck, who will fund all development and manufacturing expenses, in a deal that could be worth up to $477M in development and commercialization milestones, plus future royalties. Additionally, AVEO retains US rights to commercialize AV-299 in certain indications. Importantly, we believe the Street ascribes little or no value to AV-299, and we include no revenue related to this product in our model. However, given that it is a novel target with a strong major pharma partner, this agent could drive longer-term value for AVEO.

## AV-203

AV-203 is a monoclonal antibody targeting the ErB3 (HER3) receptor. ErB3 is a part of the ErbB family of receptors. ErB3-driven signaling pathways are thought to be associated with chemotherapy resistance in several solid tumors including breast, colon, head and neck, and non-small cell lung cancer. There are currently no approved drugs that target this receptor or the signaling pathway. In preclinical solid tumor xenograft models, AV-203 has demonstrated impressive *in vivo* efficacy.

In March 2009 AVEO entered in to a partnership with Biogen Idec around ErB3-targeting antibodies. Aveo received a $5 million upfront payment and is eligible for future developmental and commercial milestones outside of North America. According to the terms of the deal, AVEO is responsible for the development of AV-203 through the proof-of-concept clinical trials. Importantly, the company retains North American commercial rights for the drug.

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# Financial Projections

## P&L Highlights

Our forecasted revenues for 2010-15 are $30M, $75M, $109M, $178M, $291M, and $374M, respectively. We anticipate tivozanib will launch in RCC in 2012 and our 2012-15 tivozanib US sales estimates are $29M, $151M, $232M, and $299M, respectively. We expect AVEO to partner the drug in Europe and receive royalty revenues from EU sales (at a rate of roughly 25%), with the launch anticipated in 2013 and associated 2013-15 revenues of $18M, $49M, and $65M, respectively. We forecast profitability in 2015, the third full year of Tivozanib sales. Our projected 2010-15 EPS estimates are ($2.91), ($1.76), ($2.15), ($1.66), ($0.42), and $0.54. We expect net operating losses will negate taxes through this period (see Table 11).

Table 11: AVEO Pharmaceuticals: Our Operating Model

| ($ in millions except per sh data) | 2009E | 2010E | 2011E | 2012E | 2013E | 2014E | 2015E |
|---|---|---|---|---|---|---|---|
| US Tivozanib sales (RCC Only) | - | - | - | 28.7 | 150.6 | 232.1 | 299.2 |
| EU Tivozanib sales (RCC Only) | - | - | - | 0.0 | 70.4 | 197.2 | 259.0 |
| WW Tivozanib sales | - | - | - | 28.7 | 221.0 | 429.3 | 558.2 |
| | | | | | | | |
| Revenues | | | | | | | |
| Collaborative / R&D revenue | 20.8 | 30.0 | 75.0 | 80.0 | 10.0 | 10.0 | 10.0 |
| US Tivozanib sales | - | - | - | 28.7 | 150.6 | 232.1 | 299.2 |
| EU Tivozanib royalties | - | - | - | 0.0 | 17.6 | 49.3 | 64.7 |
| Total Revenues | 20.8 | 30.0 | 75.0 | 108.7 | 178.2 | 291.4 | 374.0 |
| | | | | | | | |
| Operating Expenses | | | | | | | |
| Cost of sales | - | - | - | 4.7 | 36.5 | 70.8 | 92.1 |
| Research and development | 51.8 | 102.5 | 115.0 | 135.0 | 150.0 | 165.0 | 175.0 |
| Sales, general and administrative | 10.1 | 18.0 | 22.5 | 55.0 | 60.0 | 75.0 | 85.0 |
| Total Operating expenses | 61.9 | 120.5 | 137.5 | 194.7 | 246.5 | 310.8 | 352.1 |
| | | | | | | | |
| Operating Income | (41.1) | (90.5) | (62.5) | (86.1) | (68.3) | (19.5) | 21.9 |
| Interest Income | 0.1 | 3.0 | 2.0 | 3.0 | 2.0 | 4.0 | 5.0 |
| Interest expense | (2.8) | (2.8) | (2.8) | (2.8) | (2.8) | (2.8) | (2.8) |
| Other expense | (0.3) | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Total Other Income | (3.0) | 0.2 | (0.8) | 0.2 | (0.8) | 1.2 | 2.2 |
| | | | | | | | |
| Pretax Income | (44.1) | (90.3) | (63.3) | (85.9) | (69.1) | (18.3) | 24.1 |
| Income tax (benefit) | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| | | | | | | | |
| Net Income (loss) | (44.1) | (90.3) | (63.3) | (85.9) | (69.1) | (18.3) | 24.1 |
| | | | | | | | |
| Non-GAAP EPS | (2.03) | (2.91) | (1.76) | (2.15) | (1.66) | (0.42) | 0.54 |
| Fully diluted shares outstanding | 21.7 | 31.0 | 36.0 | 40.0 | 41.5 | 43.0 | 44.5 |

Source: Company reports and J.P. Morgan estimates.

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## Balance Sheet and Cash Flow

As of September 30, 2009, AVEO had $62M in cash, cash equivalents, and marketable securities. If we assume the company burned $35M in cash out to March 2010, including the IPO the company has ~$108M (see Table 12). If we assume an estimated annual burn of $60M, then by our calculations, AVEO could have sufficient cash to get through 2011, though we formally assume an equity raise in 2011 and 2012 in our model.

Table 12: AVEO Pharmaceuticals: Projected Balance Sheet

| ($ in millions except per share data) | 2009E | 2010E | 2011E | 2012E | 2013E | 2014E | 2015E |
|---|---|---|---|---|---|---|---|
| Assets | | | | | | | |
| Cash and cash equivalents | 45.3 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Marketable Securities | 6.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Total Cash and Marketable Securities | 51.3 | 47.7 | 63.4 | 83.9 | 28.2 | 23.5 | 61.2 |
| Accounts receivable | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| Prepaid expenses and other current assets | 1.3 | 1.6 | 1.9 | 2.3 | 2.7 | 3.2 | 3.9 |
| Total Current Assets | 53.1 | 49.7 | 65.7 | 86.6 | 31.4 | 27.2 | 65.6 |
| Property, plant & equipment, net | 4.2 | 2.8 | 1.2 | (0.5) | (2.4) | (4.5) | (6.7) |
| Other assets | 1.9 | 1.9 | 1.9 | 1.9 | 1.9 | 1.9 | 1.9 |
| Restricted cash | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 |
| Total Long Term Assets | 6.8 | 5.3 | 3.8 | 2.1 | 0.2 | (1.9) | (4.2) |
| Total Assets | 59.8 | 55.1 | 69.5 | 88.7 | 31.6 | 25.3 | 61.4 |
| Liabilities and Equity | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Accounts payable | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 | 7.5 |
| Accrued expenses | 7.4 | 7.4 | 7.4 | 7.4 | 7.4 | 7.4 | 7.4 |
| Loans payable, net of discount | 7.5 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Deferred revenue | 11.8 | 11.8 | 11.8 | 11.8 | 11.8 | 11.8 | 11.8 |
| Deferred rent | 0.2 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Total Current Liabilities | 34.3 | 26.7 | 26.7 | 26.7 | 26.7 | 26.7 | 26.7 |
| Loans payable, net of current portion and discount | 12.3 | 12.3 | 12.3 | 12.3 | 12.3 | 12.3 | 12.3 |
| Deferred revenue, net of current | 23.3 | 23.3 | 23.3 | 23.3 | 23.3 | 23.3 | 23.3 |
| Deferred rent, net of current portion | 0.8 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Other liabilities | 1.2 | 1.2 | 1.2 | 1.2 | 1.2 | 1.2 | 1.2 |
| Warrants to purchase convertible preferred stock | 1.5 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Convertible preferred stock | 156.7 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Total Long Term Liabilities | 195.8 | 36.8 | 36.8 | 36.8 | 36.8 | 36.8 | 36.8 |
| Total Liabilities | 230.1 | 63.5 | 63.5 | 63.5 | 63.5 | 63.5 | 63.5 |
| Total Shareholders' Equity | (170.3) | (8.4) | 6.0 | 25.1 | (31.9) | (38.2) | (2.1) |
| Total Liabilities and Equity | 59.8 | 55.1 | 69.5 | 88.7 | 31.6 | 25.3 | 61.4 |

Source: Company reports and J.P. Morgan estimates.

**Cash Flows**

Free cash flow for AVEO is expected to be negative out to 2014 (see Table 13). We assume two additional capital raises for AVEO: $75 million in 2011 and $100M in 2012, at which point we estimate AVEO will have sufficient cash to fund operations through FY2015, when cash flow from operations is expected to turn positive.

Table 13: AVEO Pharmaceuticals: Projected Cash Flows

| ($ in millions except per share data) | 2009E | 2010E | 2011E | 2012E | 2013E | 2014E | 2015E |
|---|---|---|---|---|---|---|---|
| Cash Flows from Operating Activities: | | | | | | | |
| Net Income | (44.1) | (90.3) | (63.3) | (85.9) | (69.1) | (18.3) | 24.1 |
| Depreciation and Amortization | 1.3 | 1.4 | 1.6 | 1.7 | 1.9 | 2.1 | 2.3 |
| Stock-based compensation | 2.4 | 5.0 | 8.0 | 12.0 | 12.0 | 12.0 | 12.0 |
| Noncash interest expense | 0.7 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Loss on loan extinguishment | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Loss on disposal of property and equipment | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Remeasurement of warrants to purchase convertible preferred stock | 0.3 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Amortization of (premium) discount on investments | 0.4 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Net change in Working Capital | 29.1 | (0.4) | (0.3) | (0.4) | (0.5) | (0.5) | (0.6) |
| Net Cash From Operations | (10.0) | (84.3) | (54.1) | (72.5) | (55.6) | (4.7) | 37.7 |
| Cash Flows from Investing Activities: | | | | | | | |
| Purchases of property and equipment | (1.7) | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Purchases of marketable securities | (35.9) | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Proceeds from maturities and sales of marketable securities | 41.1 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Purchase of long-term investment | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Net Cash from Investing | 3.4 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Cash Flows from Financing Activities: | | | | | | | |
| Proceeds from issuance of convertible preferred stock, net of issuance costs | 32.9 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Proceeds from exercise of stock options and issuance of common and restricted stock | 0.2 | 80.7 | 69.8 | 93.0 | 0.0 | 0.0 | 0.0 |
| Net proceeds from issuance of loans payable | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Extinguishment of loan | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Principal payments on loans payable | (2.0) | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Repayment of capital lease and note obligations | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Net Cash from Financing | 31.0 | 80.7 | 69.8 | 93.0 | 0.0 | 0.0 | 0.0 |
| Net Increase (Decrease) in Cash | 24.5 | (3.6) | 15.7 | 20.5 | (55.6) | (4.7) | 37.7 |
| Cash and cash equivalents at beginning of period | 20.8 | 45.3 | 41.7 | 57.4 | 77.8 | 22.2 | 17.5 |
| Cash and cash equivalents at end of period | 45.3 | 41.7 | 57.4 | 77.8 | 22.2 | 17.5 | 55.2 |

Source: Company reports and J.P. Morgan estimates.

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# Valuation

Our $14 December 2010 price target for AVEO shares is supported by a revenue multiple analysis. Using a framework that is typical for emerging, small-cap biotech valuation, we apply a 5X revenue multiple to our 2013 forecasts, at the lower end of the range at which peers are currently trading (4-7X). In our model, 2013 will be the second year that tivozanib is on the US market and the first year that it launches on the EU market. We then discount back to the present at a 25% rate, which is consistent with the discount rate afforded many phase 3 trials with "de-risked" phase 2 data.

Using this methodology, we arrive at a price target of $14 for AVEO shares, which supports our Overweight rating. At this point, we think AVEO is too early in its development to yield a higher-confidence DCF or NPV analysis given the significant number of uncertainties on new indications, partnering economics, etc. Please see Table 14 below for comparable revenue multiple among peers in small-cap biotech.

Table 14: Comparative Valuation Analysis

| Company | Ticker | JPM Rating | Price Apr 19, 2010 | 52-Wk Hi | 52-Wk Lo | Mkt Cap | EV | 2012E Revs | EV/2012E Revs |
|---|---|---|---|---|---|---|---|---|---|
| Alexion | ALXN | | 54.69 | 56.30 | 32.26 | 5,001 | 4,836 | 821.1 | 5.9 |
| Allos | ALTH | OW | 8.22 | 8.79 | 5.46 | 839 | 680 | 247.2 | 2.8 |
| Acorda | ACOR | OW | 37.19 | 39.50 | 15.52 | 1,407 | 1,142 | 393.0 | 2.9 |
| AMAG | AMAG | OW | 36.04 | 58.23 | 33.11 | 620 | 540 | 184.0 | 2.9 |
| Amylin | AMLN | N* | 21.14 | 24.21 | 10.10 | 3,017 | 3,068 | 1142.8 | 2.7 |
| BioMarin | BMRN | OW* | 23.26 | 24.99 | 12.05 | 2,383 | 2,579 | 522.5 | 4.9 |
| Human Genome | HGSI | OW* | 31.49 | 34.49 | 1.16 | 5,375 | 5,255 | 1082.9 | 4.9 |
| Onyx | ONXX | OW* | 29.62 | 36.75 | 21.85 | 1,842 | 1,436 | 397.5 | 3.6 |
| OSI | OSIP | N | 59.28 | 60.42 | 27.01 | 3,808 | 3,540 | 581.7 | 6.1 |
| Vertex | VRTX | N | 40.04 | 44.24 | 25.94 | 7,427 | 6,264 | 2008.4 | 3.1 |
| United Therapeutics | UTHR | N | 58.38 | 61.97 | 27.35 | 3,148 | 2,949 | 817.8 | 3.6 |
| Mean | | | | | | 3,170 | 2,935 | | 3.9 |
| | | | | | | | | | |
| Aveo Pharma** | AVEO | OW | 8.86 | 9.61 | 8.16 | 275 | 181 | 191.5 | 0.9 |

Source: Company reports, Bloomberg, and J.P. Morgan estimates.
*Covered by Cory Kasimov. Prices as of April 19, 2010. Estimates for companies not covered are consensus estimates from Bloomberg.
**AVEO 2012 Revenue based on 2015 estimates of $374M discounted to 2012 at 25%/year.

# Management

**Tuan Ha-Ngoc**
*CEO*
Mr. Ha-Ngoc has been CEO and President of AVEO since June 2002. Prior to AVEO, Mr. Ha-Ngoc served as co-founder, President, and CEO of deNovis, a software development company for the automation of healthcare administrative functions. Previously, he was corporate vice president of strategic development for Wyeth. Mr. Ha-Ngoc serves on the boards of directors of Human Genome Sciences, Inc. and several academic and nonprofit organizations including Harvard School of Dental Medicine, Tufts School of Medicine, and MIT Koch Institute of Integrative Cancer Research.

**David Johnston**
*Chief Financial Officer*
Mr. Johnston has served as CFO since October 2007. Previously, he served as senior vice president of corporate finance at Genzyme Corporation. Mr. Johnston serves on the board of directors of Tissue Banks International.

**Elan Ezickson**
*Chief Business Officer*
Mr. Ezickson has served as chief business officer since April 2003. Prior to AVEO, he served in several senior-level positions at Biogen, including president of Biogen Canada, program executive, and associate general counsel. He also serves on the board of directors of Greater Boston Food Bank.

**William Slichenmyer, M.D., Sc.M.**
*Chief Medical Officer*
Dr. Slichenmyer has been with AVEO since September 2009 and is the company's CMO. Prior to joining AVEO, Dr. Slichenmyer served as CMO at Merrimack. Previously, he worked at Pfizer, where he served in various positions, including global head of oncology clinical development as well as positions in medical affairs and regulatory affairs.

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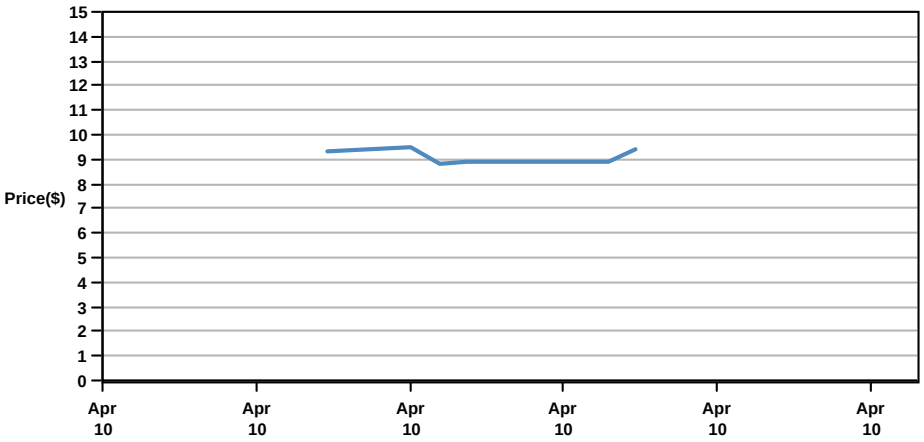
**AVEO Pharmaceuticals, Inc. (AVEO) Price Chart**




**Source: Bloomberg and J.P. Morgan; price data adjusted for stock splits and dividends.**
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