Zacks Small-Cap Research

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RestorGenex Corp. (RESX - OTC)

RESX: An In-Depth Look At RES-529…

UPDATE

Current Recommendation	**Buy**
Prior Recommendation	N/A
Date of Last Change	03/16/2015
Current Price (05/07/15)	$2.45
Target Price	**$6.50**

In March 2015, we initiated coverage of RestorGenex Corp. with a Buy rating and a $6.50 price target.

In this report, we discuss RestorGenex's lead compound, RES-529, a first-in-class inhibitor of the PI3K/AKT/mTOR signaling pathway. This pathway is implicated in cell proliferation, growth, survival, and angiogenesis. The company is studying RES-529 as a treatment for both oncology and ophthalmology indications, and is planning to initiate two Phase 1/2 clinical trials in the first half of 2016.

SUMMARY DATA

52-Week High	**$6.20**
52-Week Low	**$2.35**
One-Year Return (%)	**-59.68**
Beta	**0.64**
Average Daily Volume (sh)	**6,096**
Shares Outstanding (mil)	**19**
Market Capitalization ($mil)	**$47**
Short Interest Ratio (days)	**0.14**
Institutional Ownership (%)	**24**
Insider Ownership (%)	**20**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2015 Estimate	**N/A**
P/E using 2016 Estimate	**N/A**

Risk Level	**Above Average**
Type of Stock	**Small-Growth**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue
(In millions of $)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2014	0 A	0 A	0 A	0 A	0 A
2015	0 E	0 E	0 E	0 E	0 E
2016					0 E
2017					0 E

Earnings per Share
(EPS is operating earnings before non-recurring items)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2014	-$0.23 A	-$0.35 A	-$0.18 A	-$0.26 A	-$1.00 A
2015	-$0.20 E	-$0.22 E	-$0.22 E	-$0.23 E	-$0.88 E
2016					-$0.70 E
2017					-$0.65 E

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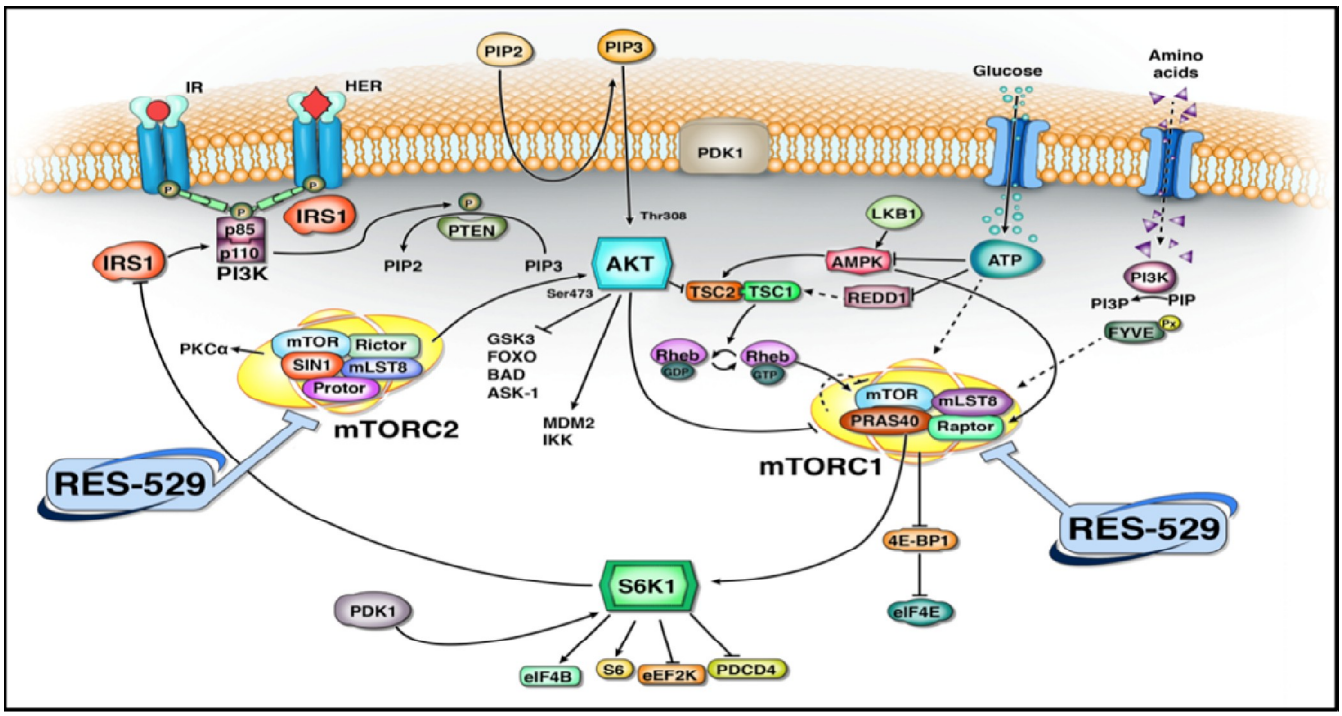
WHAT'S NEW

RestorGenex (RESX) is a specialty pharmaceutical company developing treatments for ophthalmology, oncology, and dermatology. The company has two proprietary compounds under development, RES-529 and RES-440. For the purpose of this article, we will discuss only RES-529, a drug that has completed two Phase 1 trials in Age-Related Macular Degeneration (AMD) and a number of preclinical studies supporting its use in the treatment of glioblastoma multiforme (GBM).

RES-529 targets the PI3K/AKT/mTOR signaling pathway that is implicated in a number of cellular processes, including cell growth, proliferation, differentiation, motility, angiogenesis, and survival. Mutations and amplification in the pathway has been implicated in a number of different pathological conditions, most notably cancer. The mammalian target of rapamycin (mTOR) is a protein kinase that binds to different regulatory subunits to form the mTORC1 and mTORC2 complexes. The protein was originally discovered through work with the antifungal compound rapamycin, which is an inhibitor of the mTORC1 complex. While shown to be effective against a number of cancer cell lines *in vitro*, many cancers develop resistance to rapamycin treatment through activation of the mTORC2 complex. RES-529 targets both the mTORC1 and mTORC2 complexes, interfering with the ability of mTOR to bind to the different components of each complex. This feature diminishes the potential for resistance to develop, and could potentially be a more potent therapeutic approach. Preclinical studies show that RES-529 inhibits angiogenesis and decreases vascular permeability while also inhibiting the growth of glioma tumors *in vivo*.

PI3K Signaling Pathway – A Quick Scientific Rundown Of The Target

The phosphatidylinositol 3-kinase (PI3K) pathway is a key signal transduction system that links multiple cell receptors to many essential cellular functions; it is one of the most commonly activated signaling pathways in human cancers. The pathway is involved in a number of cellular processes such as cell growth, proliferation, differentiation, motility, angiogenesis, and survival. Several pathway components, including PI3K, AKT, and mTOR are potential therapeutic targets with many small molecule inhibitors currently in development or clinical trials.



PI3K Signaling Pathway. *Source*: RestorGenex Corp.

…PI3K signaling and angiogenesis…

Angiogenesis (formation of new blood vessels) is an important physiological process that has been implicated in a number of pathological conditions, most notably in cancer. Vascular endothelial growth factor (VEGF) is a potent angiogenic factor whose effects on endothelial cells are mediated in part by the PI3K pathway. There are five members in the VEGF family: VEGFA, VEGFB, VEGFC, VEGFD, and placenta growth factor (PGF), although VEGFA is the most well-characterized and is commonly referred to as simply VEGF.

VEGF expression is increased through activation of the PI3K signaling pathway via upregulation of hypoxia-inducible factor 1 (HIF-1) (Zhong *et al*., 2000). In addition, VEGF expression can also be increased via PI3K signaling that is independent of HIF-1 (Maity *et al*., 2000). Thus, targeting the PI3K signaling pathway can have a direct effect on angiogenesis, as shown by inhibition of EGFR (a receptor that activates the PI3K pathway) in many different tumor types (Ciardiello *et al*., 2001; Pore *et al*., 2006).

…PI3K signaling targeting compounds…

Upregulation of the PI3K/AKT/mTOR signaling pathway is common in a variety of proliferative disorders, thus a large number of therapeutic candidates have been advanced into the clinic that target the various components of the pathway.

AKT Inhibitors: AKT is involved in a number of facets of tumorigenesis, such as anti-apoptosis, cell cycle progression, and the stimulation of angiogenesis (Bhutani *et al*., 2013). There are a number of AKT inhibitors in development; however, the FDA has approved only one thus far, Impavido® (miltefosine), for the treatment of leishmaniasis. For a detailed overview of AKT inhibitors in cancer treatment, we encourage investors to read Pal *et al*., 2010.

PI3K Inhibitors: While PI3K activity is typically tightly regulated in normal cells, it is recognized that up to one-third of all human cancers are associated with deregulation of the PI3K signaling pathway. Thus, PI3K is now seen as a viable target for anti-cancer therapy (Akinleye *et al*., 2013). At least 15 agents are currently in various stages of clinical development, each with favorable safety, efficacy, pharmacokinetic, and pharmacodynamic profiles. The first FDA approved PI3K inhibitor was Zydelig® (idelalisib), which was approved in 2014 for patients who suffer from chronic lymphocytic leukemia, relapsed follicular B-cell non-Hodgkin lymphoma, or small lymphocytic lymphoma and have received at least two prior systemic therapies.

mTOR Inhibitors: Since mTOR signaling is involved in cell growth, proliferation, and survival, it has been the subject of intense therapeutic interest for a number of years. The discovery of mTOR and an understanding of its basic biological functions was greatly facilitated by the use of rapamycin (sirolimus), a novel antifungal agent that was isolated from the bacterium *Streptomyces hygroscopicus,* a microbe found in the soil of Easter Island (Vézina *et al*., 1975). Rapamycin binds to the protein FKBP12, allowing the FKBP12-rapamycin complex to bind to the mTORC1 complex (Tsang *et al*., 2007). However, rapamycin does not have an acute affect on mTORC2 outside of long-term treatment of some cell types (Sarbassov *et al*., 2006).

While originally developed as an antifungal treatment, that indication was subsequently abandoned after it was discovered that rapamycin had potent immunosuppressive and antiproliferative properties. It was originally approved by the U.S. Food and Drug Administration (FDA) in 1999 for the prophylaxis of organ rejection in patients receiving renal transplants and is sold under the brand name Rapamune®.

The antiproliferative activities of rapamycin were shown by screening the compound against a variety of human tumor cell lines in the National Cancer Institute's Development Therapeutics Program. Rapamycin was found to inhibit the growth of mammary, colon, and melanoma cell lines (Douros *et al*., 1981). Due to rapamycin's low oral bioavailability, a number of rapamycin analogs (rapalogs) have been developed and two of these compounds have been approved for use in humans:

- ✓ Temsirolimus (CCI-779) is an intravenous drug that is approved for the treatment of renal cell carcinoma and marketed under the name Torisel®.

- ✓ Everolimus (RAD001) is approved both for the prevention of organ transplant rejection as well as a treatment for kidney cancer, pancreatic cancer, and breast cancer. The drug is sold under the name Zortress® in transplantation medicine and Afinitor® in oncology.

One of the drawbacks to rapamycin and the rapalogs is that there is a negative feedback loop associated with phosphorylated S6K, and since this is not present when mTORC1 is inhibited, the upstream regulators of mTORC1 become more active (Veilleux *et al*., 2010). In addition, since there is no effect on mTORC2, AKT continues to be activated, and this serves as a mechanism to enhance cells survival when mTORC1 is inactivated (Wan *et al*., 2007).

…Second-generation mTOR inhibitors…

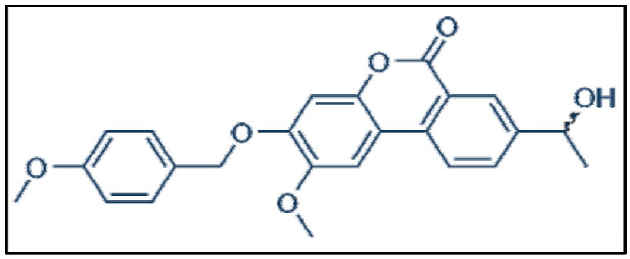
To overcome the issues associated with rapamycin and other mTORC1 selective inhibitors, a number of "second generation" inhibitors that target the catalytic domain of mTOR have been developed (Zhang *et al*., 2011). These compounds can be broken down into dual mTOR/PI3K inhibitors or dual mTORC1/mTORC2 inhibitors and have been tested against a wide range of tumor types.

mTOR/PI3K Inhibitors: Thus far only a few dual mTOR/PI3K compounds have entered early clinical testing. XL765 (mTOR, IC_{50} = 157 nM; PI3Kα, IC_{50} = 39 nM) was the first compound to report Phase 1 results, with five out of 19 patients showing disease stabilization for at least 3 months, and two having a sustained response for longer than 6 months (Molckovsky *et al*., 2008). GDC0980 (mTOR, IC_{50} = 17.3 nM; PI3Kα, IC_{50} = 4.8 nM) showed broad activity in a number of different cancer models, including breast, ovarian, lung, and prostate, and appears to be active against both the wild-type PI3K pathway as well as in tumor cells bearing mutations to PI3K, PTEN, or K-RAS (Wagner *et al*., 2009; Makker *et al*., 2014).

mTORC1/mTORC2 Inhibitors: A majority of these compounds are directed against the ATP-binding domain of mTOR, and as a result block both mTOR complexes. PP242 is more effective than rapamycin in inducing apoptosis of leukemia cells and has a much weaker immunosuppressive effect (Janes *et al*., 2010). INK128 has shown an ability to affect prostate cancer metastases *in vivo*, a condition for which no cure exists (Hsieh *et al*., 2012). AZD8055 has shown broad activity against a range of human tumor types (Chresta *et al*., 2010) and is more effective than everolimus (RAD001) against endocrine-resistant breast cancer cell lines (Jordan *et al*., 2014).

…RES-529 is a dual mTORC1/mTORC2 inhibitor…

RestorGenex is developing RES-529, a derivative of a non-steroidal estrogen antagonist that maintains antiproliferative activity while retaining no ability to inhibit binding to the estrogen receptor. This drug is a derivative of 3-hydroxy dibenzo[*b,d*]pyran-6-one, which was previously described to share structural similarities with the potent anti-angiogenic and antitumor compound 2-methoxyestradiol, and to exhibit selective antiproliferative activity for endothelial cells (Schmidt *et al*., 2003).



RES-529. *Source:* Selleckchem.com

In summary, while there are a plethora of compounds targeting the PI3K signaling pathway, due to the central role the pathway plays in a number of cellular processes and conditions, coupled with the lack of approved agents that can target both the mTORC1 and mTORC2 complexes, it seems clear to us that there exists a need for better treatment options that target this critical signaling pathway.

INDICATION I: Wet Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is a common eye condition that is the leading cause of irreversible vision loss in people over the age of 50, and a reason for more than 46% of cases of severe vision loss (Mavija *et al*., 2014). AMD may affect one or both eyes, or each eye may have varying degrees of AMD. The condition advances at different rates, with some patients experiencing very limited vision loss while in others the disease progresses faster and may lead to a loss of vision in one or both eyes. As AMD progresses, a blurred area near the center of vision is a common symptom.

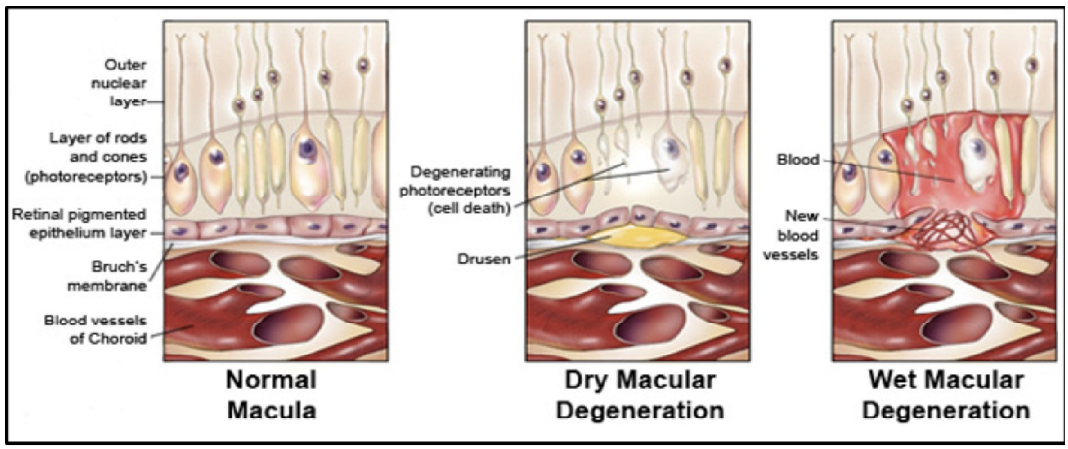
Over time, the blurred area may grow larger or a person may develop blank spots in their central vision. This may also be accompanied by objects not appearing as bright as they once were. While AMD itself does not lead to complete blindness, the loss of central vision can have a severe impact on everyday activities such as the ability to see faces, drive, read, or write.



***Source*: Centralvision.com**

The disease is caused by a number of diverse heterogeneous pathological processes, with advanced age being the primary determinant. For example, approximately 8.7% of the elderly population worldwide is affected by AMD, particularly in developed countries (Cascella *et al*., 2014). Other risk factors for developing the condition are smoking (Thornton *et al*., 2005), diet (Kaushik *et al*., 2008), and genetics (Seddon *et al*., 2005). The number of people worldwide with AMD is expected to increase to 196 million in 2020 and 288 million in 2040 (Wong *et al*., 2014).

Depending on the presence or absence of choroidal neovascularization (the growth of new blood vessels from the choroid, or vascular layer of the eye, into the sub-retinal space), AMD can be divided into two types: dry AMD or wet AMD. Dry AMD can be divided into three stages, early, intermediate, and late, depending upon the size and number of drusen under the retina. In wet AMD (which is another form of late AMD), abnormal blood vessels begin to grow (angiogenesis) behind the retina under the macula due to increased expression of vascular endothelial growth factor (VEGF). These blood vessels are typically very fragile and as a result they can leak blood and fluid. The blood and fluid raises the macula from its normal place at the back of eye, with the damage to the macula occurring very rapidly. Thus, a person may lose their central vision very quickly. For this reason, wet AMD is considered advanced AMD and is a more severe form than dry AMD.



***Source*: BrightField® Foundation**

…Current treatment options for wet AMD…

There are currently three treatment options for wet AMD: laser surgery, photocoagulation, and anti-VEGF therapy. None of these treatments are cures for wet AMD; however, these treatments may slow the rate of vision decline or stop further vision loss. Nevertheless, patients may still have progressively worse vision even with treatment. For this article, we will primarily focus on anti-VEGF therapy, as laser photocoagulation is becoming less popular due to its limited effectiveness and high side-effects and photodynamic therapy has moved from front-line to adjuvant alongside of anti-VEGF.

VEGF plays a key role in the pathogenesis of wet AMD. Increased VEGF production is a consequence of oxidative cell stress, which results in the proliferation of newly formed blood vessels. Anti-VEGF therapies bind to and inhibit VEGF thus blocking the formation and growth of these new blood vessels. A paradigm shift in the treatment of AMD occurred over the past decade with the advent of VEGF inhibitors, beginning with the approval of Macugen® in 2004, followed by Lucentis® (ranibizumab) in 2006, and the subsequent off-label use of Genentech's oncology drug, Avastin® (bevacizumab), a far cheaper and similarly efficacious alternative to Lucentis®.

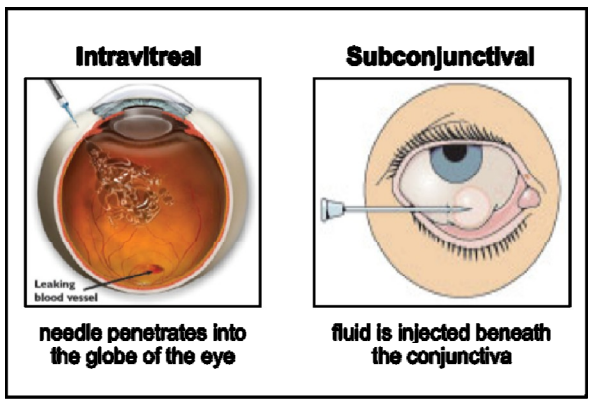
For example, results from randomized clinical trials have been conducted comparing bevacizumab to ranibizumab for neovascular age-related macular degeneration. Results have been published in the New England Journal of Medicine (Martin *et al*., 2011) and the Journal of Ophthalmology (Martin *et al*., 2012). The primary impetus for significant off-label use of bevacizumab is cost. According to Ron Afashari, MD of the Yale School of Medicine and Director of the Yale Retina Service, Avastin® (bevacizumab) costs approximately $30 to $50 per dose when used off-label, whereas Lucentis® (ranibizumab) costs approximately $2,000 per dose! Roche sold an estimated $1.7 billion worth of Lucentis® in the U.S. in 2014, with Novartis selling another $2.4 billion in areas outside the U.S., mainly Europe.

Aflibercept (Eylea®, Regeneron Pharmaceuticals) injection is another relatively new product that was approved by the FDA for the treatment of wet AMD in November 2011. It is composed of the extracellular VEGF-binding domains VEGF receptors 1 and 2 fused to the Fc portion of human IgG1. Since its approval, Eylea® has gained significant market share on Lucentis® and Avastin® for AMD, primarily because the drug can be given every eight weeks after the first three months of treatment, as opposed to the monthly injections with the aforementioned two. The drug is also approved for use in the treatment of patients with Macular Edema following Central Retinal Vein Occlusion (CRVO) and Diabetic Macular Edema (DME). Elyea® 2014 worldwide sales were approximately $2.8 billion, with $1.7 billion of that in the U.S.

Anti-VEGF therapies have proven to be beneficial for some patients with wet AMD; however, rapid drug clearance necessitates frequent in-clinic injections of anti-VEGF treatments into the vitreous of the eye. This is associated with a high clinical cost, limited patient independence, and an increased risk of infection, endophthalmitis, retinal detachment or cataracts (Georgopoulos *et al*., 2009; Sampat *et al*., 2010).

…Why RES-529 May Be A Better Option…

One of the key clinical advantages that RES-529 may have over currently available therapies such as Lucentis® and Eylea® is that it is being developed as a subconjuctival injection as opposed to an intravitreal injection. We believe that, assuming comparable efficacy, just about everyone would prefer a subconjuctival administration over intravitreal. Thus, we view this as a means for RestorGenex to differentiate RES-529 from currently available wet AMD treatments as we believe that a novel wet AMD treatment with non-intravitreal administration and less frequent dosing would likely gain wide acceptance.

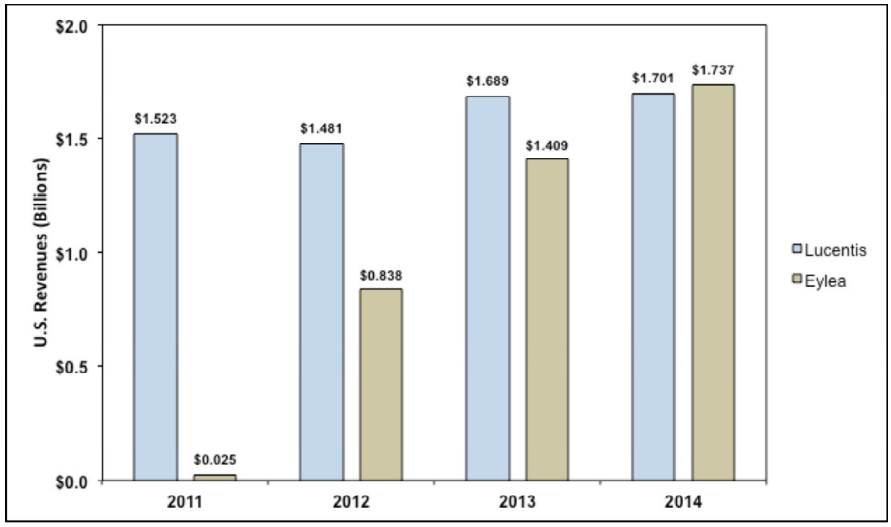


***Source*: RestorGenex Corp.**

…Wet AMD market…

According to the BrightFocus® Foundation, approximately 11 million individuals in the U.S. have some form of AMD. Due to the aging population, this number is expected to double to 22 million by 2050. Wet AMD accounts for just 10% of these cases, but is responsible for greater than 90% of legal blindness due to the disease.

As discussed earlier, there are multiple types of treatments available for wet AMD. The anti-VEGF therapies (particularly ranibizumab and aflibercept) dominate the market. In 2014, Lucentis® (marketed by Roche in the U.S. and Novartis in the rest of the world) and Eylea® (marketed by Regeneron in the U.S. and Bayer in the rest of the world) had worldwide revenues of $4.1 and $2.8 billion, respectively, for all approved indications (wet AMD, DME, and CRVO). As shown in the following chart, since launching in 2011, Eylea® has rapidly caught up to Lucentis® in terms of revenues in the U.S. and in 2014 surpassed Lucentis® for the first time.

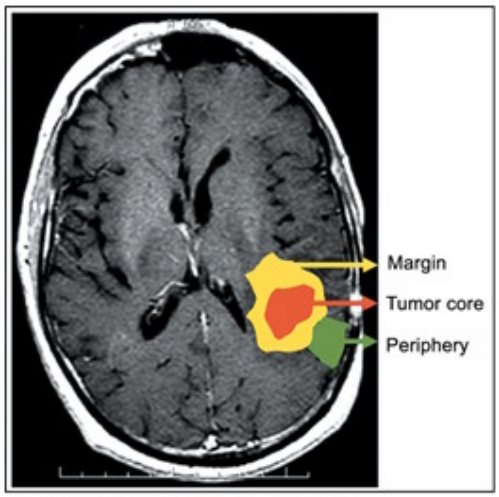


Source: Zacks SCR / Bautz

Given the limitations of the currently available therapeutics and the increased incidence of wet AMD, we believe there is ample opportunity for a successful wet AMD therapy to become a blockbuster medication with revenues in excess of $1 billion.

INDICATION II: Glioblastoma Multiforme

Glioblastoma multiforme (GBM) is a grade IV brain tumor characterized by a heterogeneous cell population with a number of negative attributes. GBM cells are typically genetically unstable (thus prone to mutation), highly infiltrative, angiogenic, and resistant to chemotherapy (Wen *et al*., 2008). The mutations typically found in GBM allow the tumor to grow and thrive in a hypoxic environment (Furnari *et al*., 2007). Both activating mutations and loss of tumor suppressor genes give rise to the highly complex and difficult to treat nature of the disease. For example, approximately 50% of GBM tumors have amplification of the epidermal growth factor receptor (EGFR), which can then induce activation of the PI3K signaling pathway (Taylor *et al*., 2012).



MRI of GBM tumor indicating sampling areas.
Source: Wei *et al*., 2010

GBM is classified into two major subclasses (primary or secondary) depending upon the clinical properties as well as the chromosomal and genetic alterations that are unique to each class. Primary GBM arises *de novo* from normal glial cells and typically occur in those over the age of 40, while secondary GBM arises from transformation of lower grade tumors and is usually seen in younger patients (Ladha *et al*., 2010). Primary GBM is believed to account for approximately 95% of all GBMs.

While GBM is the most common form of primary brain tumor involving glial cells, it is still relatively rare as approximately 24,000 people in the U.S. were diagnosed with some form of malignant brain cancer in 2014. Gliomas account for approximately 80% of malignant brain cancers, with GBM accounting for approximately 45% of gliomas. The median age of GBM diagnosis is approximately 65 years, with the incidence of GBM in those over 65 increasing rapidly as shown by a doubling in incidence from 5.1 per 100,000 in the 1970's to 10.6 per 100,000 in the 1990's (Chakrabarti *et al*., 2005). Those diagnosed with the disease have a very grim prognosis, with the median survival time of untreated patients being only 4.5 months. Current standard of care treatment only provides 12-14 months of survival time after diagnosis (Johnson *et al*., 2012).

…Current treatments for GBM…

Standard of care for GBM tumors always begins with surgical resection of the tumor. This is performed both to alleviate the symptoms associated with the disease as well as to facilitate treatment of any residual tumor cells. Even with advances in surgical technique, complete removal of the tumor with clean margins is almost never possible, as the tumors are highly infiltrative and typically extend into the normal brain parenchyma. Due to this, almost all GBM patients have recurrence of the tumor, with 90% occurring at the primary site (Wen *et al*., 2008).

Due to the invasive nature of the tumors, surgical resection is followed by radiotherapy coupled with the use of chemotherapeutic agents. Radiotherapy involves the administration of irradiation to the whole brain (Grossman *et al*., 2004). While nitrosoureas were the most common chemotherapeutic agents used for a number of decades, in 1999 temozolomide (TMZ) became available and is now a part of the standard of care. This is due to a clinical trial that showed the addition of TMZ to surgery and radiation increased median survival in newly diagnosed GBM patients to 14.6 months compared to 12.1 months for the surgery and radiation only group (Stupp *et al*., 2005).

Most chemotherapeutic drugs have a limited ability to cross the blood brain barrier (BBB), thus a strategy to circumvent this was the development of dissolvable chemotherapy wafers (Gliadel®) that could be placed in the tumor bed following surgical resection (Perry *et al*., 2007). Gliadel® contains the nitrosourea chemotherapeutic agent carmustine that is released for several weeks, in contrast to systemically administered carmustine that has a very short half-life. While Gliadel® wafers were shown to be safe, the drugs' addition to radiation and TMZ did not result in a statistically significant increase in survival, (De Bonis *et al*., 2012).

GBM tumors show increased expression of VEGF (Bao *et al*., 2006), and bevacizumab has been approved by the FDA for the treatment of recurrent GBM. A Phase 2 study found that bevacizumab treatment in patients with recurrent GBM increased six-month progression-free survival from a historical 9-15% to 25% with overall six-month survival of 54% (Raizer *et al*., 2010). Another Phase 2 study showed that recurrent GBM patients treated with bevacizumab at a lower dose but a higher frequency had even higher six-month progression-free survival of 42.6% (Friedman *et al*. 2009).

While bevacizumab has shown success in recurrent GBM, it is not utilized in newly diagnosed patients as two separate clinical trials showed no difference in overall survival in patients treated with radiation, TMZ, and bevacizumab compared to patients treated with only radiation and TMZ (Gilbert *et al*., 2014; Chinot *et al*., 2014). Interestingly, bevacizumab treatment did result in an increase in progression free survival in both studies; however, why the effect in progression free survival did not translate to an increase in overall survival is unclear. In addition, Gilbert *et al*. reported that patients treated with bevacizumab had an increased symptom burden, a worse quality of life, and a decline in neurocognitive function.

…Resistance mechanisms to treatment…

Clearly, development of effective GBM therapeutics has been quite challenging. This is in part due to a number of mechanisms intrinsic to GBM tumors that make them very difficult to treat:

- Highly infiltrative: GBM tumors infiltrate into the surrounding healthy tissue of the brain, making complete surgical resection virtually impossible. The aggressive nature of GBM cells means that a small number of cells left behind after surgery are capable of continued growth, leading to the poor prognosis for GBM patients.

- Hypoxia: A majority of the GBM tumor environment is hypoxic, or lacking in adequate oxygen supply. This lack of oxygen limits the effectiveness of radiation as the amount of DNA-damaging free radicals generated by radiation treatment is decreased.

- Hydrostatic pressure: The vasculature of GBM tumors is highly irregular and leaky, resulting in very high hydrostatic pressure. This makes drug delivery to the tumor difficult, as the therapeutic agents are not able to infiltrate deep into the tumor.

- DNA damage repair: Resistance to TMZ is mediated by the DNA repair protein methyl guanine methyl transferase (MGMT). High levels of MGMT activity in GBM cells blunt the therapeutic effect of alkylating agents (such as TMZ). Conversely, methylation of the promoter of the *MGMT* gene results in loss of MGMT expression and decreased DNA repair activity (Qian *et al*., 1997). Methylation status is highly predictive of survival in newly diagnosed GBM patients, with a 2004 study showing 18-month survival of 62% for patients with a methylated MGMT promoter compared to just 8% for patients without a methylated MGMT promoter (Hegi *et al*., 2004).

…GBM therapies under development…

There are a number of companies developing GBM therapies, as shown by a search on clinicaltrials.gov that yields over 300 results for "glioblastoma multiforme" and "open trials". In addition to the therapeutics previously mentioned, current trials are examining the following:

- DCVax®-L: This product uses a patient's dendritic cells as a vaccine. After surgery, a portion of the tumor that is removed from the patient is combined with the patient's dendritic cells to "educate" the dendritic cells to respond to tumor antigens. The "educated" dendritic cells are then reintroduced into the patient, at which point the dendritic cells stimulate B- and T-cell responses to the tumor. The treatment is currently being tested in a Phase 3 clinical trial in conjunction with standard of care (NCT00045968). The trial's sponsor is Northwest Biotherapeutics.

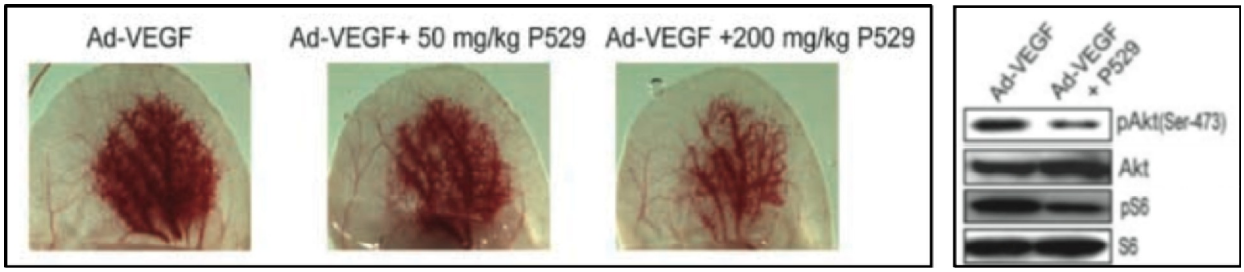
- Rindopepimut: This is a single-peptide based vaccine that targets the 13-amino acid sequence EGFRvIII receptor antigen. EGFRvIII is a mutated form of EGFR that constitutively activates the receptor and is present in 25-33% of GBM tumors (Pelloski *et al*., 2007). Two Phase 2 clinical trials showed that vaccination with rindopepimut in addition to maintenance TMZ resulted in median overall survival of 23.6 and 26 months (Sampson *et al*., 2010; Sampson *et al*., 2011). Rindopepimut is currently being tested in a Phase 3 trial as an addition to the current standard of care involving TMZ treatment (NCT01480479). The trial's sponsor is Celldex Therapeutics.

- Nivolumab/Ipilimumab: These are monoclonal antibodies directed against immune regulatory proteins. Nivolumab is directed against programmed death-1 (PD-1) while ipilimumab targets cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4). Both agents have activity in treating metastatic melanoma, with ipilimumab (Yervoy®) approved for that indication. While there is currently no clinical data for either molecule in GBM patients, preclinical data shows that both agents are active in orthotopic murine models of glioblastoma (Fecci *et al*., 2007; Zeng *et al*., 2013). Nivolumab is being compared to bevacizumab in a Phase 3 trial involving recurrent GBM patients while simultaneously being tested in combination with ipilimumab (NCT02017717). The trial's sponsor is Bristol-Myers Squibb.

- Veliparib: This is a small molecule inhibitor of poly ADP ribose polymerase (PARP), an enzyme involved in DNA single-strand break repair. Preclinical data showed that veliparib enhanced killing of four GBM cell lines when used in conjunction with radiotherapy and TMZ (Barazzuol *et al*., 2013). The compound is currently being tested in a Phase 2/3 study in patients with newly diagnosed GBM (NCT02152982). The trial's sponsor is AbbVie.

…RES-529 inhibits angiogenesis and reduces vascular permeability…

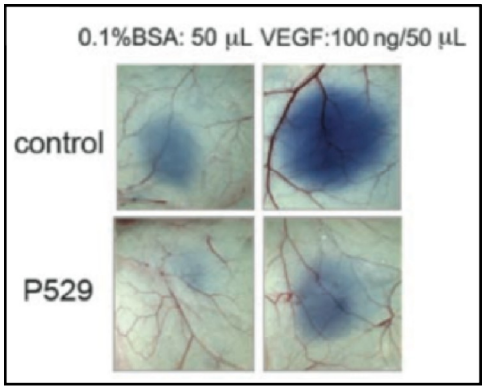
RestorGenex has performed a number of pre-clinical studies that have shown RES-529 is able to inhibit angiogenesis induced by VEGF, thus indicating that the compound could be beneficial to treat diseases with dependency upon VEGF-induced angiogenesis, such as wet AMD and GBM. The following figure shows the results of an experiment where VEGF was injected into mice ears to induce angiogenesis, with the mice being concurrently treated with different doses of RES-529 (P529 in the figure).



***Source*: Xue *et al*. 2008**

The results show that RES-529 inhibits angiogenesis in a dose dependent manner, and it also inhibited phosphorylation of AKT at serine 473 (pAktSer-473) and phosphorylation of ribosomal protein S6 kinase (pS6), indicative of an inhibition of both mTORC1 (lack of pS6) and mTORC2 (lack of pAktS473).

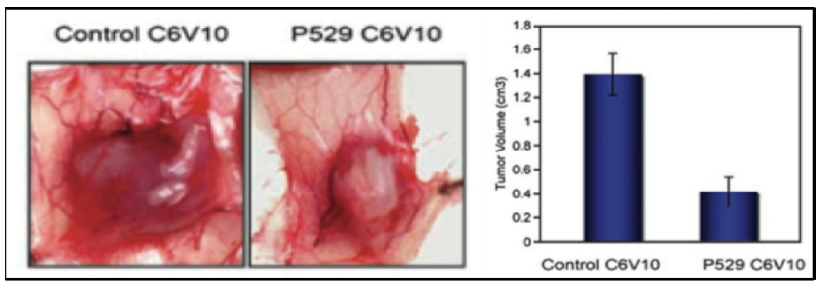
In addition to affecting angiogenesis, RES-529 appears to affect vascular permeability, which is the capacity of a blood vessel wall to allow for the flow of small molecules in and out of the vessel. Increased VEGF would be expected to increase vascular permeability, and when this occurs in the presence of a tumor it allows for increased nutrient uptake and growth. Thus, a treatment that decreases vascular permeability would be expected to decrease the amount of nutrients available to a tumor, thus inhibiting growth. The following figure shows the result of RES-529 in the Miles assay, which measures vascular permeability through the retention of a blue dye in the vasculature. The assay was performed with either a control protein (bovine serum albumin, BSA) or VEGF to show increased permeability with VEGF treatment. Addition of RES-529 (P529 in the figure) results in a greatly decreased staining, indicating that RES-529 is directly reducing VEGF-driven vascular permeability.



***Source*: Xue *et al*., 2008**

…RES-529 inhibits glioma tumor growth…

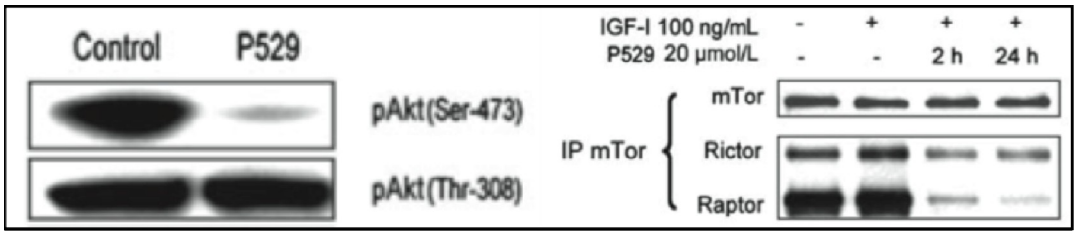
RES-529 was tested as a potential cancer therapeutic with experiments involving the C6 rat glioma cell line (Benda *et al*., 1968). For these studies, the C6 variant C6V10, which is transfected with exogenous mouse VEGF (Benjamin *et al*., 1997), was utilized as it has previously been found to have a more accurate vascular pathology representative of high-grade glioblastoma, including glomeruloid vessels, which are not commonly found in mouse tumors. Nude mice were pre-treated for one week with 200 mg/kg RES-529 before C6V10 cells were injected subcutaneously, with treatment continuing for 21 days. The following figure shows that tumors from mice treated with RES-529 (P529 in the figure) grew an average of 70% less than control tumors.



***Source*: Xue *et al*., 2008**

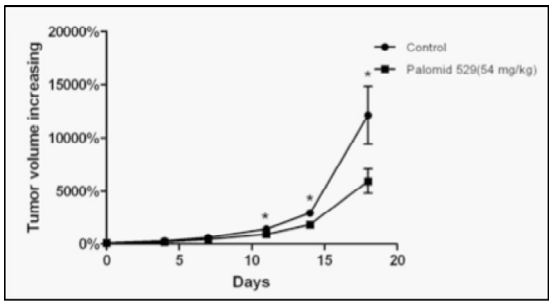
Analysis of tumor lysates showed that RES-529 treatment dramatically reduced phosphorylation of AKT at serine 473; however, it did not affect phosphorylation of AKT at threonine 308, suggesting that RES-529 is an inhibitor of mTORC2. Based on its structure, RES-529 is likely not an ATP-competitive inhibitor, thus suggesting that the compound may inhibit the protein-protein interactions within the mTORC complexes.

To examine this further, immunoprecipitation experiments were performed with C6V10 cells. The following figure shows that RES-529 inhibited the association of mTOR with both Rictor and Raptor in the presence of insulin growth factor-1 (IGF-1), suggesting that RES-529 inhibits both the TORC1 and TORC2 complexes.



***Source:* Xue *et al.*, 2008**

Lastly, an effective GBM treatment needs to be capable of crossing the blood-brain barrier (BBB), which is an impediment to a number of potential therapeutics. The BBB is formed by the brain micro-vasculure endothelial cells. These cells contain tight junctions and require substances to use tightly regulated influx transporters (such as GLUT1 for glucose) to gain access to the brain. Substances that do not have such transporters can only gain access to the brain through passive diffusion, and this is highly dependent on the lipophilicity of the compound (Muldoon *et al*., 2007). Even substances that cross the BBB may not accumulate in the brain thanks to a set of ATP-binding cassette (ABC) drug efflux transporters, particularly ABCB1 and ABCG2, two efflux transporters known to limit the accumulation of lipophilic anti-cancer agents and small molecule inhibitors (Agarwal *et al*., 2010). Results with RES-529 show that the compound does not interact with ABCB1 or ABCG2 and that those efflux transporters do not restrict the brain penetration of RES-529 (Lin *et al*., 2013). This was exhibited by treating mice harboring intracranial GBM tumors with RES-529 (Palomid 529), which significantly inhibited tumor growth compared to control mice, as shown in the following figure.



***Source:* Lin *et al.*, 2013**

…GBM is an orphan disease…

Malignant brain cancers are diagnosed in approximately 24,000 individuals every year, making it an "orphan disease". The Orphan Drug Act of 1983 was designed to provide financial incentives for and to reduce the costs associated with developing drugs for rare diseases and disorders. A "rare disease or disorder" is defined by the Act as affecting fewer than 200,000 Americans at the time of designation or one for which "there is no reasonable expectation that the cost of developing and making available in the United States…will be recovered from sales in the United States." A sponsor must request that the FDA designate a drug currently under development for a "rare disease or condition" as an orphan drug, and if the FDA agrees that the drug and indication meet the criteria set forth in the Act, certain incentives become available.

In January 2015, RestorGenex announced that RES-529 has been granted orphan drug designation for GBM. This entails RestorGenex to all the incentives listed above. The most beneficial of the Orphan Drug incentives include: 1) written recommendations from the U.S. FDA on non-clinical and clinical development, 2) seven years of market exclusivity once approved, 3) a tax credit in the amount of 50% of qualified clinical testing expenses, and 4) waiver of PDUFA fees.

Similar laws have been passed in other major markets such as Europe and Japan. In Europe, orphan drug status is not associated with tax breaks or subsidies at the European Union level, but the exclusivity period is longer at 10 years. In Japan, the exclusivity period is also 10 years, and takes special significance, as the approval times are so long that many drugs are reaching the end of their patent life when finally approved.

…GBM market analysis…

It is predicted there will be approximately 23,000 malignant brain tumors diagnosed in the U.S. in 2015 (CBTRUS). Gliomas make up approximately 80% of all malignant brain tumors, with GBM comprising approximately 45% of all gliomas (Ostrom *et al*., 2014). Thus, we estimate that there will be approximately 8,300 cases of GBM diagnosed in the U.S. in 2015. Worldwide, there were an estimated 250,000 malignant brain tumors diagnosed in 2012 (GLOBOCAN 2012). There were a similar percentage of gliomas and GBM worldwide, thus we estimate that 90,000 individuals were diagnosed with GBM in 2012.

The FDA originally approved TMZ in 1999 for the treatment of GBM. Schering-Plough marketed the drug until their 2009 merger with Merck. At the time of the merger, TMZ (sold as Temodar®) was a blockbuster medication, with 2008 revenues of just over $1 billion. Patent exclusivity for Temodar® (marketed as Temodal® outside the US) ended in 2009 in the EU and in 2014 in the US. However, based upon an agreement between Merck and Teva Pharmaceuticals, a generic version of Temodar® was launched in the US in August 2013. Thus, sales have declined from a high of $1.065 billion to in 2010 to $708 million in 2013.

Avastin® is one of the world's top-selling medications, with annual sales close to $6 billion. However, given the small patient population associated with GBM, sales for Avastin® in this indication are only approximately $170 million per year.

RES-529 development plans

RestorGenex is planning to develop RES-529 as a treatment for both wet AMD and GBM. The company plans on finalizing the CMC work of the active pharmaceutical ingredient (API) so that final IND-enabling studies can be performed in 2015. This will enable the filing of the IND for both indications in the first half of 2016.

- For wet AMD, two Phase 1 clinical trials have been performed with RES-529. In the first company-sponsored study (Protocol P52901), fifteen patients were injected intravitreally with varying doses of RES-529 from 0.004 mg up to 0.5 mg. In the second study (Protocol 11-EI-0066), sponsored by the National Eye Institute, five patients refractory to anti-VEGF treatment were dosed with subconjunctival injections of 2 mg once a month for three months (Dalal *et al*., 2013). Both studies showed RES-529 to be well tolerated with no serious adverse events. For the next step in development as a treatment for wet AMD, a Phase 1/2 clinical trial will be performed in 2016 to assess the safety, tolerability, and clinical efficacy of RES-529. In addition, the maximum tolerated dose will be established for subconjuctival administration.

- For GBM, a Phase 1/2 clinical trial will be performed in 2016 to assess the maximum tolerated dose in GBM patients along with early efficacy signals. The company also has plans to initiate clinical trials in other oncology indications, most likely prostate, lung cancer, and breast cancer, using the maximum tolerated dose established in the GBM trial.

Conclusion

RestorGenex currently has a market cap of approximately $46 million. The company currently has approximately $22 million in cash and cash equivalents as of the end of 2014. We see this as plenty of capital to get the requisite IND enabling studies completed as well as initiate the Phase 1/2 clinical trials. For example, cash burn in the fourth quarter 2014 was only $2.0 million.

The company is targeting three multi-billion dollar indications, wet AMD, GBM, and acne (not discussed in this article). As evidenced by the recent launch of Regeneron's Eylea®, a successful wet AMD treatment can generate revenues in excess of $1 billion shortly after approval. With the limited treatment options for GBM, a successful therapeutic could also potentially generate over $1 billion in peak revenues, as Temodar® did before losing patent protection. Lastly, a differentiated acne therapeutic, RES-400, is a potential $300 million opportunity. While an investment in an early stage biotechnology company is very high risk, with multiple high revenue opportunities an investment in RestorGenex has an enormous potential return.

…Valuation Methodology…

For both indications for RES-529, we estimate that RestorGenex would initiate a Phase 2b study in 2017, with a Phase 3 trial commencing in 2018, and an NDA filing in 2020 with approval of RES-529 in 2021. For RES-440, RestorGenex could initiate a Phase 3 study in 2017, an NDA filing in 2018, and obtain approval in 2019. For each indication we apply a 22% discount rate and give a probability of success of 15% for wet AMD and 10% each for GBM and acne. For RES-529, we estimate peak revenues of $1.5 billion for wet AMD and $650 million for GBM. At this point we are modeling for RestorGenex to market RES-529 in the U.S. and to partner for selling in the rest of the world, with a 15% royalty rate on sales.

For RES-440, we are estimating peak revenues of $450 million, and just as with RES-529 we model for RestorGenex to market the compound in the U.S. and partner for sales in the rest of the world. Please note that we plan to author a second article on RES-400 in the near future.

Adding up our “sum-of-parts” analysis gives an estimated net present value for each indication of $125 million for wet AMD, $25 million for GBM, and $30 million for acne. Adding in the company’s current cash total and an estimate $25 million in capital requirements gives a net present value for the company of approximately $175. Dividing this total by the fully diluted share count of 26.75 million shares leads to a fair value of approximately $6.50 per share. Thus, at the current stock price of only $2.45 per share, we believe investment in RestorGenex is warranted and could prove to be highly lucrative.

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PROJECTED FINANCIALS

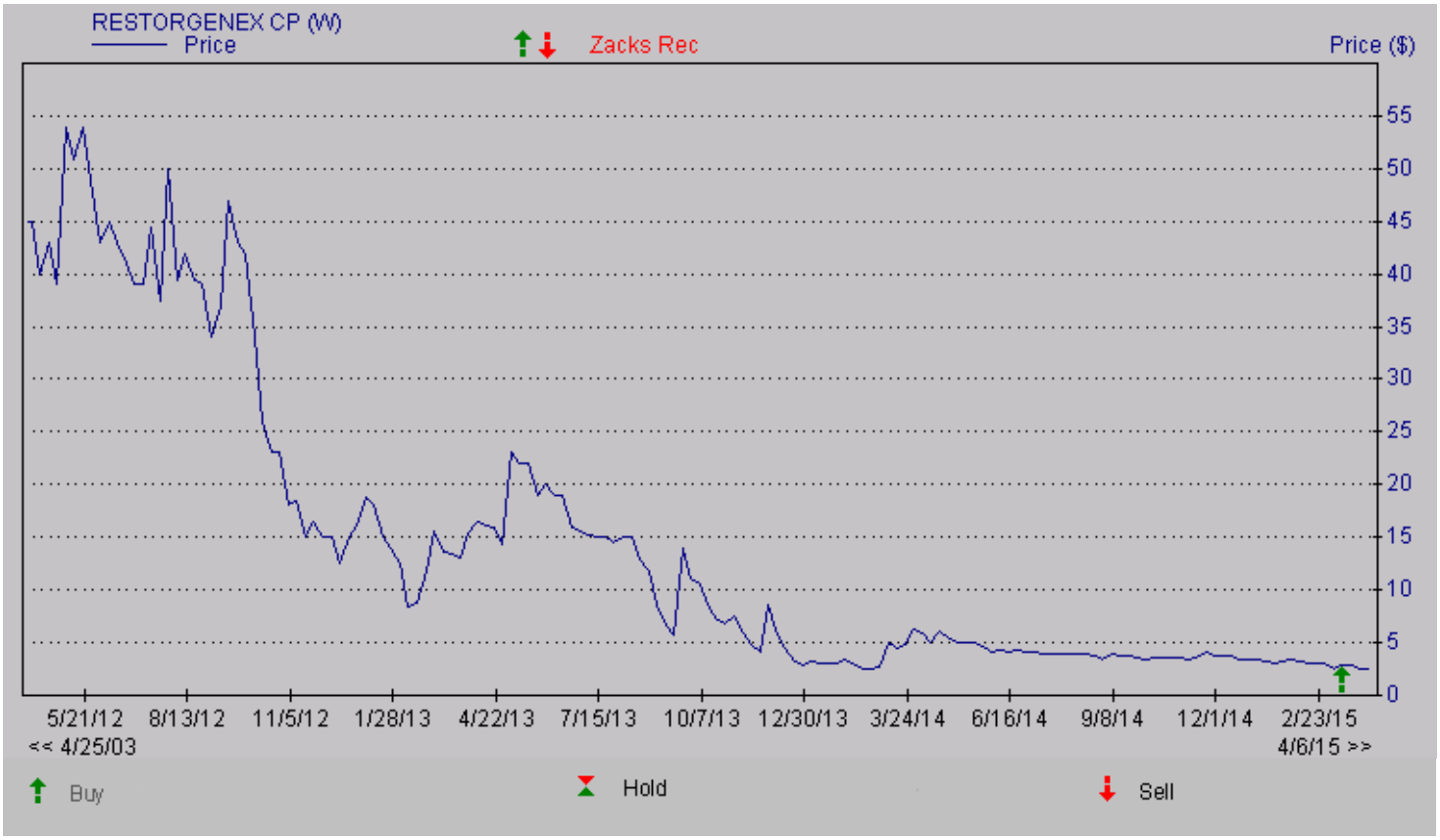
RestorGenex Corp.
Income Statement

RextorGenex Corp.	2014 A	Q1 E	Q2 E	Q3 E	Q4 E	2015 E	2016 E
Total Revenues	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth	-	-	-	-	-	-	-
Cost of Sales	$0	$0	$0	$0	$0	$0	$0
Product Gross Margin	-	-	-	-	-	-	-
Research & Development	$2.9	$1.2	$1.4	$1.5	$1.5	$5.6	$6.0
General & Administrative	$4.8	$1.1	$1.2	$1.2	$1.3	$4.8	$5.5
Other Expenses	$7.0	$1.0	$1.0	$1.0	$1.0	$4.0	$4.0
Operating Income	($14.6)	($3.3)	($3.6)	($3.7)	($3.8)	($14.4)	($15.50)
Operating Margin	-	-	-	-	-	-	-
Non-Operating Expenses (Net)	($2.6)	($0.5)	($0.5)	($0.5)	($0.5)	($2.0)	($2.0)
Pre-Tax Income	($17.2)	($3.8)	($4.1)	($4.2)	($4.3)	($16.4)	($17.5)
Income Taxes Paid	($2.8)	$0	$0	$0	$0	$0	$0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	**($14.4)**	**($3.8)**	**($4.1)**	**($4.2)**	**($4.3)**	**($16.4)**	**($17.5)**
Net Margin	-	-	-	-	-	-	-
Reported EPS	**($1.00)**	**($0.20)**	**($0.22)**	**($0.22)**	**($0.23)**	**($0.88)**	**($0.70)**
YOY Growth	-	-	-	-	-	-	-
Basic Shares Outstanding	14.3	18.6	18.6	18.7	18.7	18.7	25.0

Source: Zacks Investment Research, Inc. *Jason Napodano, CFA*

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