Zacks Small-Cap Research

March 16, 2015
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RestorGenex Corp. (RESX - OTC)

RESX: Initiating Coverage of RestorGenex Corp.; Deap Pipeline and Attractive Valuation…

Current Recommendation	**Outperform**
Prior Recommendation	N/A
Date of Last Change	03/16/2015
Current Price (03/16/15)	$2.80
Target Price	**$6.50**

INITIATION

We are initiating coverage of RestorGenex Corp. with an Outperform rating and a $6.50 price target.

RestorGenex's lead compound, RES-529, is 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. In addition, the company is developing a first-in-class "soft" anti-androgen for the treatment of acne. All told, the company is targeting three potential multi-billion dollar markets.

SUMMARY DATA

52-Week High	**$6.30**
52-Week Low	**$2.38**
One-Year Return (%)	**-37.08**
Beta	**0.55**
Average Daily Volume (sh)	**14,804**
Shares Outstanding (mil)	**19**
Market Capitalization ($mil)	**$52**
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 E	0 E
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	-$0.19 E	-$0.91 E
2015	-$0.08 E	-$0.09 E	-$0.10 E	-$0.10 E	-$0.37 E
2016					-$0.41 E
2017					-$0.45 E

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WHAT'S NEW

Initiating Coverage

We are initiating coverage of RestorGenex Corp. (RESX) with an Outperform rating and a $6.50 price target.

RestorGenex 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. RES-529 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. A number of pathway components, including the proteins PI3K, AKT, and mTOR, are potential therapeutic targets with many small molecule inhibitors currently under development.

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 as both the mTORC1 and mTORC2 complexes are inhibited in the presences of RES-529. Preclinical studies showed that RES-529 inhibits angiogenesis and decreases vascular permeability while also inhibiting the growth of glioma tumors *in vivo*.

RestorGenex is developing RES-529 as a therapy for both wet age related macular degeneration (AMD), a degenerative eye condition that is the leading cause of vision loss in people over the age of 50, and glioblastoma multiforme (GBM), the most common form of malignant brain cancer with a five year survival rate of approximately 5%. Both of these conditions are dependent upon PI3K signaling and aberrant blood vessel formation, or angiogenesis.

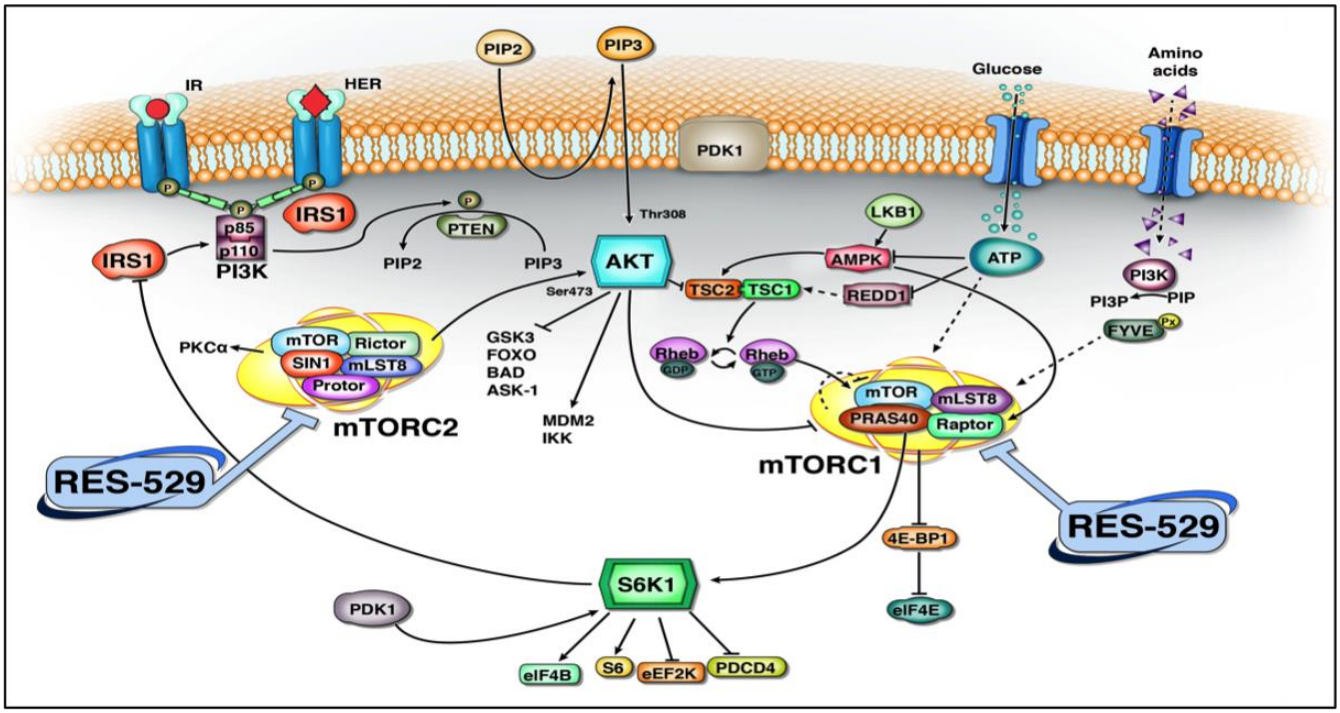
In addition to RES-529, RestorGenex is also developing RES-440, a first-in-class "soft" anti-androgen for the treatment of acne vulgaris, or acne, which is a skin condition that causes pimples. While not life threatening, acne can have a dramatically negative effect on a person's life, and patients are continuously looking for better treatment options for the condition. Acne is in part a result of androgenic stimulation of sebaceous glands that results in an increase in sebum, or oil, on the skin. The sebum can form plugs in hair follicles that leads to the formation of pimples. RES-440 is designed to be a potent anti-androgen, which should limit the effect of excess androgens on sebum formation. The compound is rapidly metabolized locally to an inactive metabolite, thus decreasing any potential adverse systemic effects that are common with other anti-androgen therapies.

RestorGenex currently has approximately $20 million in cash and cash equivalents. The company plans to finish preclinical and toxicology studies for both RES-529 and RES-440 during 2015 with a goal to file an investigational new drug (IND) application on each compound in 2016 for glioblastoma and acne, respectively. The company already has on file an active IND with the FDA for the use of RES-529 for the use of AMD. Management plans to initiate Phase 1/2 studies for both compounds in 2016; three clinical studies in total.

INVESTMENT THESIS

PI3K Signaling Pathway

The phosphatidylinositol 3-kinase (PI3K) pathway is a key signal transduction system that links multiple cell receptors to many essential cellular functions and 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.



PI3K Signaling Pathway. *Source*: RestorGenex Corp.

Several pathway components, including PI3K, AKT, and mTOR are potential therapeutic targets with many small molecule inhibitors currently in development or clinical trials:

- **PI3Ks**: A family of enzymes that phosphorylate the 3-position of the inositol ring of phosphatidylinositol to produce the second messenger PIP3, which binds Protein Kinase B (AKT) and leads to its activation (Okkenhaug, 2013).
- **AKT**: Three members of the AKT family (AKT1, AKT2, and AKT3) have been identified with AKT1 playing a key role in cellular metabolism and survival. These proteins are serine/threonine protein kinases that are activated through phosphorylation of threonine 308 by PDK1 or serine 473 by the mTORC2 complex (Sarbassov *et al*., 2005). Activated AKT can then go on to activate/deactivate its myriad of substrates, one of which is mTOR.
- **mTOR**: The mammalian target of rapamycin (mTOR) is a protein kinase that binds to different regulatory subunits to produce the mTORC1 and mTORC2 complexes, each with distinct signaling functions (Ballou et al., 2008).
- **mTORC1**: This complex is composed of the proteins mTOR, Raptor, mLST8, PRAS40, and DEPTOR and is responsible for phosphorylating ribosomal protein S6 kinase (S6K) at threonine 389 and the translation repressor 4EBP1 (Wang *et al*., 2012). One of the roles of the complex is to activate production of cellular proteins. The mTORC1 complex is inhibited by rapamycin.
- **mTORC2**: This complex is composed of the proteins mTOR, Rictor, mLST8, DEPTOR, PROTOR, and mSIN1 and is responsible for phosphorylating AKT at serine 473 (Wang *et al*., 2012). The biological function of mTORC2 is less clear than mTORC1; however, it appears to control cell survival and organization of the cell cytoskeleton. This complex is insensitive to inhibition by rapamycin.

…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. While there are too many compounds currently in clinical development to discuss here, interested readers are encouraged to read the review by Pal *et al*. for a detailed overview of AKT inhibitors in cancer treatment (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…

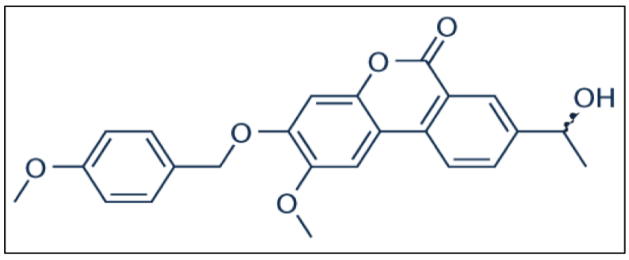
To overcome the issues associated with rapamycin and other mTORC1 selective inhibitors, a number of "second generation" inhibitors that target the catalytic domain of mTOR have been developed (Zhang *et al*., 2011). These compounds can be broken down into dual mTOR/PI3K inhibitors or dual mTORC1/mTORC2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

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, **WE CONCLUDE** that there exists a need for better treatment options that target this critical signaling pathway.

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



RES-529. *Source*: Selleckchem.com

RestorGenex is developing RES-529 (8-(1-Hydroxy-ethyl)-2-methoxy-3-(4-methoxy-benzyloxy)-benzo[*c*]chromen-6-one), a derivative of a nonsteroidal 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 (referred to in prior studies as Palomid 529 or P529) has been studied in a number of preclinical studies in both ophthalmology and oncology, a few of which we highlight below.

Ophthalmology

Lewis *et al*., 2009: RES-529 is reported to have a long ocular half-life, and because it is an inhibitor of the AKT/mTOR pathway that controls a number of cellular processes, it was investigated what the effect of RES-529 treatment would be on sub-retinal scar formation and photoreceptor survival induced by retinal detachment. Results showed that a single injection of RES-529 can significantly reduce photoreceptor cell death, the amount of intraretinal proliferation, and the number and size of sub-retinal scars, indicating that it may be useful for treating proliferative diseases associated with retinal detachment surgery and ensuing photoreceptor cell death.

Oncology

Xue *et al*., 2008: This study first showed that RES-529 is an inhibitor of both mTORC1 and mTORC2. The compound was shown to inhibit tumor growth, angiogenesis, and reduced vascular permeability in an *in vivo* model of glioblastoma. Like rapamycin, RES-529 showed the ability to normalize tumor vasculature; however, in addition the compound blocked phosphorylation of AKT on serine 473, consistent with blocking mTORC2 activity.

Diaz *et al*., 2009: This study evaluated the hypothesis that RES-529 would enhance the effect of radiotherapy (RT) in an *in vivo* model of prostate cancer, as the AKT pathway is known to be involved in radio-resistance. The results showed that RES-529 potentiates the effect of RT via inhibition of AKT phosphorylation, but also through other cancer-related pathways involving MMP-2, MMP-9, and vascular endothelial growth factor (VEGF) that reduced proliferation rates and promoted apoptosis.

Gravina *et al*., 2011: The aim of this study was to evaluate the use of RES-529 in association with docetaxol (DTX) and cisplatin (CP) for the treatment of hormone-refractory prostate cancer. Results showed that RES-529 synergized with both DTX and CP, with the greatest results seen when prostate cancer cells were treated sequentially with either DTX or CP followed by RES-529. In addition, *in vivo* treatment with a combination of RES-529 and DTX or CP increased the percentage of complete responders and reduced the number of mice with tumor progression.

Gravina *et al*., 2014: This study aimed to identify the molecular mechanisms through which RES-529 exerts its radio-sensitizing properties in a panel of prostate cancer models. Results showed that RES-529 downregulated proteins associated with DNA double-strand break repair. In addition, treatment with RES-529 promoted pro-apoptotic and autophagic events.

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. Other risk factors for developing the condition are smoking (Thornton *et al*., 2005), diet (Kaushik *et al*., 2008), and genetics (Seddon *et al*., 2005).

Approximately 8.7% of the elderly population worldwide is affected by AMD, particularly in developed countries (Cascella *et al*., 2014). 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).

AMD ultimately affects the central area in the ocular posterior segment of the retina, known as the *macula lutea* (Parmeggiani *et al*., 2012). This area of the retina, the macula, is essential for seeing fine details in objects straight ahead. The most common pathological hallmarks of the disease are drusen (aggregates of extracellular material) and the growth of choroid vessels. Excessive amounts of drusen and neovascularization causes chronic changes of the macula and in particular of the retinal pigment epithelium (RPE), choriocapillaries (CC), photoreceptors (rods and cones), and Bruch's membrane (BrM) (Spraul *et al*., 1996).

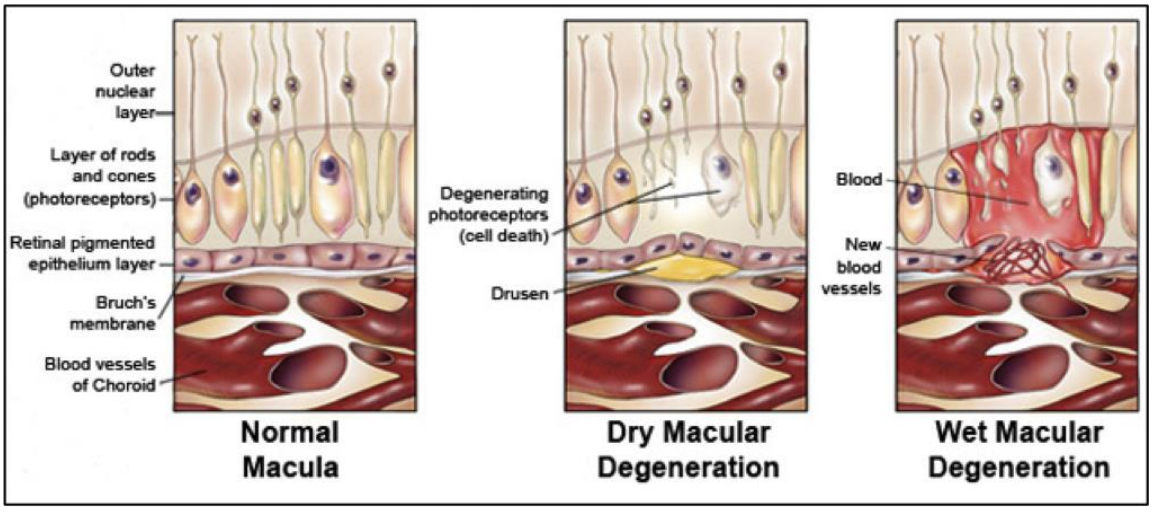
Depending on the presence or absence of choroidal neovascularization (the growth of new blood vessels from the choroid, or vascular layer of the eye, into the sub-retinal space), AMD can be divided into two types: dry AMD or wet AMD. Dry AMD can be divided into three stages, depending upon the size and number of drusen under the retina, with excessive drusen between the RPE and CC hampering the transport of oxygen and nutrients, which degenerates the RPE and photoreceptor system.

- Early AMD: Individuals with early AMD have several small or a few medium-sized drusen. At this stage there are no symptoms and no vision loss.

- Intermediate AMD: People with intermediate AMD have either many medium-sized drusen or one or more large drusen. Some people may see a blurred spot in the center of their vision or require more light for reading and other tasks.

- Late AMD: In addition to drusen, people with advanced dry AMD have a breakdown of light-sensitive cells and supporting tissue in the central retinal area. This breakdown can cause a blurred spot in the center of their vision, which over time may get bigger and darker, thus reducing more of their central vision. In addition, some people may have difficulty reading or recognizing faces until they are very close.

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.

Laser photocoagulation: For nearly twenty years the only treatment option available to those with wet AMD was laser photocoagulation. Compromised spots within the blood vessels of the retina are specifically targeted with a laser that causes clots and halts fluid leakage. Ultimately, this leads to improved oxygen supply to the retina and reduced downstream neovascularization. However, this treatment is not without side effects, namely damage to surrounding healthy tissue that can result in a small "blind spot" where the laser has scarred the retina. In addition, this surgery is only suitable for a small number of patients with wet AMD, particularly those where the leaky blood vessels have developed away from the fovea, or central part of the macula. Lastly, the risk of new blood vessels forming after treatment is quite high, with repeated treatments often necessary.

Photodynamic therapy: This treatment, approved by the FDA in 2000, couples the use of a "cold" laser of a specific wavelength along with an injectable drug (verteporfin, Visudyne®) to destroy new blood vessels. The compound is administered via infusion and approximately 15 minutes later a laser is shined into the eye for 90 seconds. The light activates the drug, which results in the generation of cytotoxic oxygen free radicals that selectively damage neovascular endothelial cells leading to thrombus formation and specific occlusion of choroidal neovascular vessels in subfoveal lesions. The treatment is typically combined with the use of intravitreal triamcinolone or anti-VEGF therapeutics.

VEGF-Inhibitors: 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®. Anti-VEGF medications quickly became the front-line therapy as clinical trials demonstrated clear improvements in visual function as compared to other therapies.

- ✓ Pegaptanib sodium (Macugen®, Valeant Pharma) is an anti-VEGF aptamer, a small piece of RNA that self-folds into a shape that binds to and blocks the effects of VEGF165, one isoform of the VEGF family of molecules. Results from two Phase 3 clinical trials demonstrated that pegaptanib efficiently stabilized visual acuity in approximately 70% of treated patients; however the effect only lasted one year. Since the advent of more effective VEGF inhibitors, pegaptanib has very limited market share.

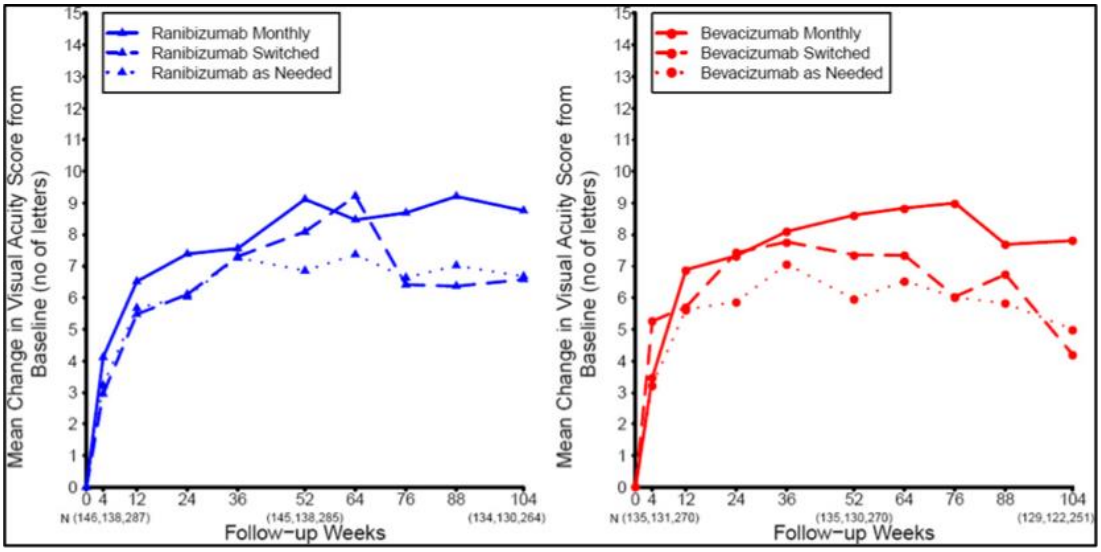
- ✓ Ranibizumab (Lucentis®, Genentech) is an antibody fragment that also binds and blocks the effects of VEGF. Unlike pegaptanib, ranibizumab binds and inhibits all isoforms of VEGF. Lucentis® is approved by the FDA for the treatment of AMD, macular edema following central vein occlusion, and diabetic macular edema (DME). We discuss the efficacy of ranibizumab below.

- ✓ Bevacizumab (Avastin®, Genentech) is the full antibody from which ranibizumab is derived. This anti-VEGF molecule is FDA approved for systemic treatment of metastatic colon cancer, but not for any ophthalmology indications. Its use in conditions such as AMD, diabetic retinopathy, and DME is currently off-label. The efficacy of Avastin® in AMD is comparable to that of Lucentis®. We discuss this below.

Avastin® vs. Lucentis®: 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). A total of 1,185 patients with wet AMD were enrolled in the clinical trial. A total of 1,107 of the 1,185 were followed for two years. At enrollment, patients were assigned to four treatment groups defined by drug (ranibizumab or bevacizumab) and dosing regimen (monthly or as needed). At one year, patients initially assigned to monthly treatment were reassigned randomly to monthly or as-needed treatment, without changing the drug assignment.

According to published results, among patients following the same regimen for 2 years, mean gain in visual acuity was similar for both drugs (bevacizumab-ranibizumab difference, -1.4 letters; 95% confidence interval [CI], -3.7 to 0.8; p=0.21). Mean gain was greater for monthly than for as-needed treatment (difference, -2.4 letters; 95% CI, -4.8 to -0.1; p=0.046).

The proportion without fluid ranged from 13.9% in the bevacizumab-as-needed group to 45.5% in the ranibizumab monthly group (drug, p=0.0003; regimen, p<0.0001). Switching from monthly to as-needed treatment resulted in greater mean decrease in vision during year two (-2.2 letters; p=0.03) and a lower proportion without fluid (-19%; p=0.0001). Rates of death and arteriothrombotic events were similar for both drugs (p=0.60). The proportion of patients with one or more systemic serious adverse events was higher with bevacizumab than ranibizumab (39.9% vs. 31.7%; adjusted risk ratio, 1.30; 95% CI, 1.07-1.57; p=0.009). Most of the adverse events have not been associated previously with systemic therapy targeting vascular endothelial growth factor (VEGF).



Source: Martin *et al*., 2012

Ranibizumab and bevacizumab had similar effects on visual acuity over a 2-year period. Treatment as needed resulted in less gain in visual acuity, whether instituted at enrollment or after 1 year of monthly treatment. There were no differences among the two drugs in rates of death or arteriothrombotic events. The interpretation of the persistence of higher rates of serious adverse events with bevacizumab is uncertain because of the lack of specificity to conditions associated with inhibition of VEGF.

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.

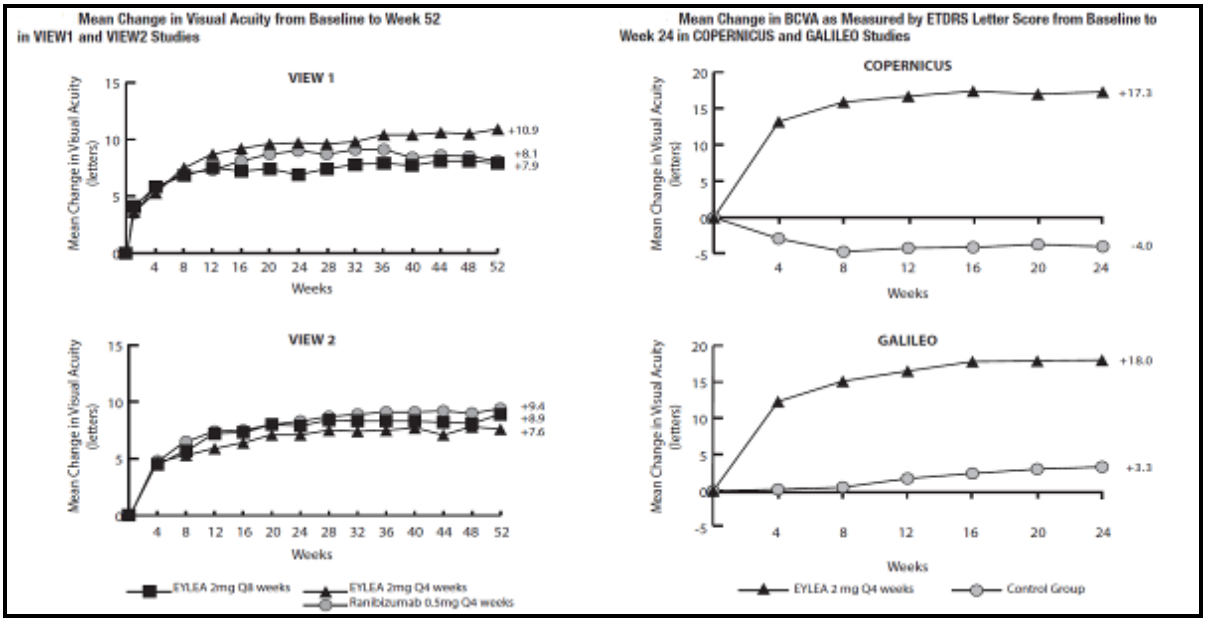
Aflibercept (Eylea®, Regeneron Pharmaceuticals) injection is a relatively new product that was approved by the FDA for the treatment of wet AMD in November 2011. It is composed of the extracellular VEGF-binding domains VEGF receptors 1 and 2 fused to the Fc portion of human IgG1. Since its approval, 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.

To gain approval, Regeneron conducted two Phase 3 studies in AMD, VIEW-1 and VIEW-2, and two additional Phase 3 studies, COPERNICUS and GALILEO in macular edema following CRVO. The data below highlights the primary efficacy findings for Elyea® in both AMD and MD-CRVO:

Eylea®	AMD Studies				MD-CRVO Studies			
	VIEW-1		VIEW-2		COPERNICUS		GALILEO	
	Eylea 2 mg Q4	Lucentis 0.5 mg Q4	Eylea 2 mg Q4	Lucentis 0.5 mg Q4	Eylea 2 mg Q4	Control	Eylea 2 mg Q4	Control
Full Set Analysis	N=304	N=304	N=309	N=291	N=114	N=73	N=103	N=68
% of patients who maintained visual acuity (<15 letters BCVA loss)	95%	94%	95%	95%	56%	12%	60%	22%
Mean change in BCVA as measured by ETDRS letter score	+10.9	+8.1	+7.6	+9.4	+17.3	-4.0	+18.0	+3.3
% of patients who gained ≥15 letters of vision from baseline	38%	31%	29%	34%	-	-	-	-

Q4 = Dosing every 4 weeks, BCVA = Best Correct Visual Acuity
ETDRS = Early Treatment Diabetic Retinopathy Study, Time = 52 wks for AMD, 24 wks for DME

Source: Elyea® Prescribing Information



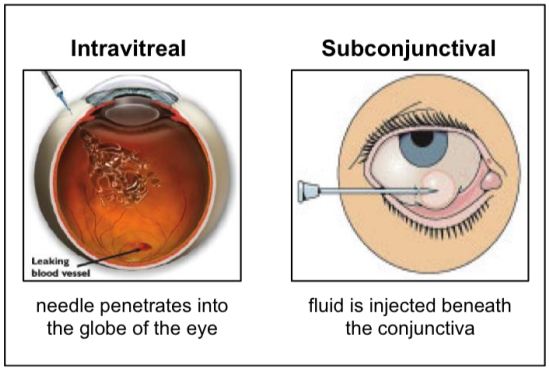
Source: Eylea® Prescribing Information

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, 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.

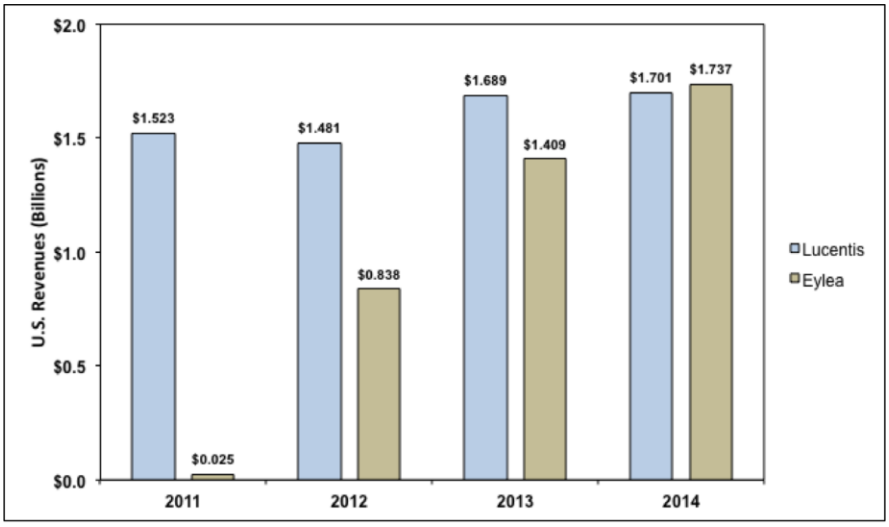


Source: RestorGenex Corp.

…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.

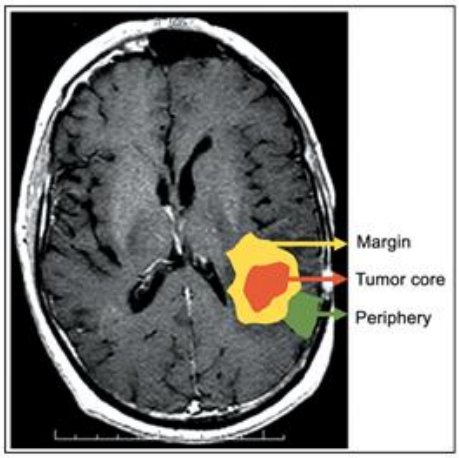


Source: Zacks SCR / Bautz

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: As discussed above, 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).

Based on the aforementioned difficulties in therapeutic development, the limited treatment options, the grim prognosis for GBM patients, and the intrinsic resistance mechanisms, **WE CONCLUDE** that there is a significant unmet medical need for more efficacious GBM therapies.

…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.

…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 including:

- ✓ The FDA must provide the sponsor with "written recommendations for the non-clinical and clinical investigations (based on the information available at the time of the request)… that would be necessary for approval of such drug for such disease or condition…"

- ✓ For a period of seven years post-approval, the FDA may not approve an application from a different sponsor for the "same drug" for the same disease or condition. For biological treatments, the FDA defines same drug to mean one that contains the "same principle molecular features." The 7-year exclusivity period conferred by orphan drug status is important because patent protection and Hatch-Waxman data exclusivity have limited effectiveness in excluding competitors from introducing equivalent drugs with slightly different structures. An exception is provided by any change that leads to improved safety or efficacy.

- ✓ Grants and contracts are available to defray the costs of development. For 2013-17, the amount appropriated is $30 million per year, which is a fairly modest sum but could make a significant difference for a small company such as RestorGenex.

- ✓ A tax credit in the amount of 50% of qualified clinical testing expenses is established by related legislation (Title 26 Part 1-28). The tax credits can be rolled forward by up to 15 years for companies that have no tax liability in the year in which expenses are occurred (e.g., pre-revenue biotech companies).

- ✓ Waiver of PDUFA fees. For FY 2014, these are $2.17 million for full NDAs, a huge benefit for a company with limited financial resources.

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.

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. However, RES-529 is not the only compound in development for treating GBM that has been granted orphan drug designation, as rindopepimut, DCVax®-L, and veliparib have all also been granted orphan drug designation for treating GBM.

…GBM market analysis…

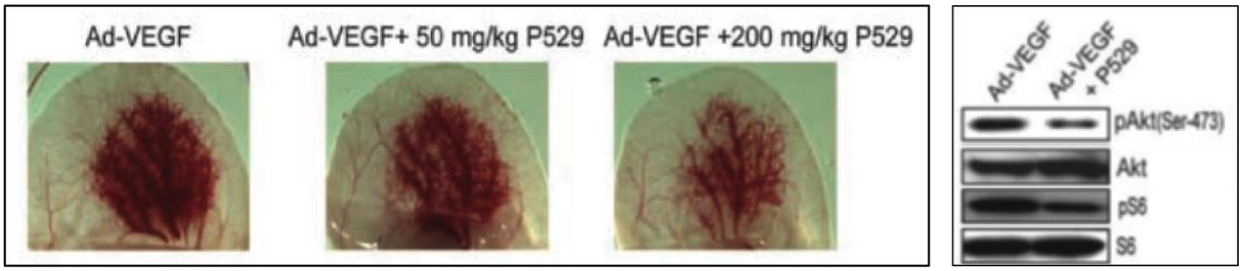
It is predicted there will be approximately 23,000 malignant brain tumors diagnosed in the U.S. in 2015 (CBTRUS). Gliomas make up approximately 80% of all malignant brain tumors, with GBM comprising approximately 45% of all gliomas (Ostrom *et al*., 2014). Thus, we estimate that there will be approximately 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 inhibits angiogenesis and reduces vascular permeability…

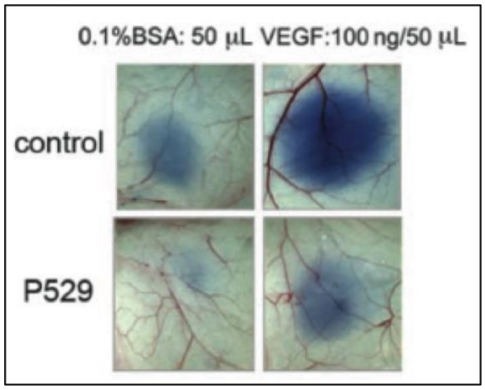
RestorGenex has performed a number of pre-clinical studies that have shown RES-529 is able to inhibit angiogenesis induced by VEGF, thus indicating that the compound could be beneficial to treat diseases with dependency upon VEGF-induced angiogenesis, such as wet AMD and GBM. The following figure shows 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).

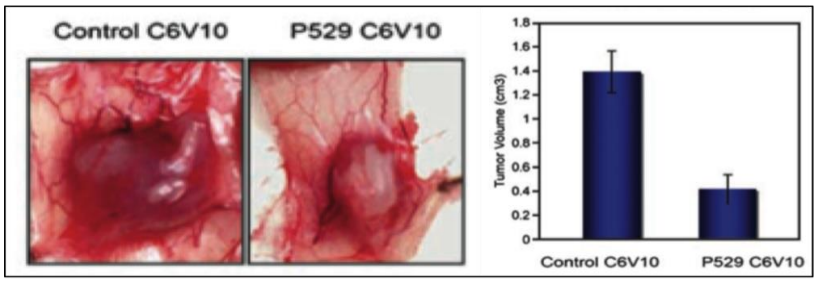
In addition to affecting angiogenesis, RES-529 appears to affect vascular permeability, which is the capacity of a blood vessel wall to allow for the flow of small molecules in and out of the vessel. Increased VEGF would be expected to increase vascular permeability, and when this occurs in the presence 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…

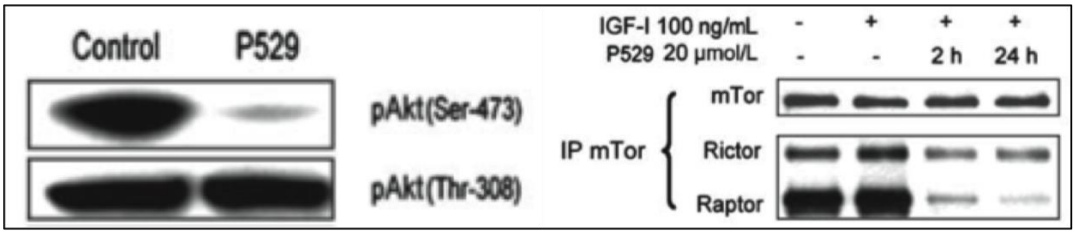
RES-529 was tested as a potential cancer therapeutic with experiments involving the C6 rat glioma cell line (Benda *et al*., 1968). For these studies, the C6 variant C6V10, which is transfected with exogenous mouse VEGF (Benjamin *et al*., 1997), was utilized as it has previously been found to have a 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

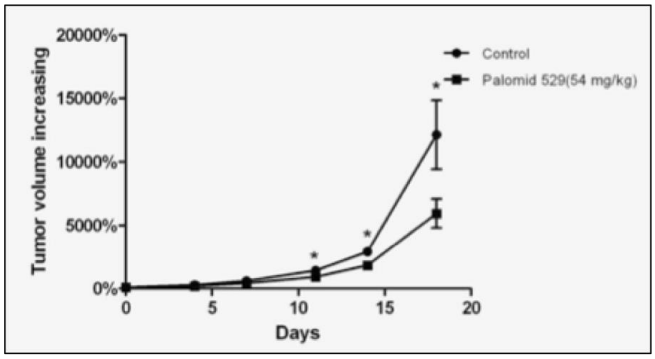
Analysis of tumor lysates showed that RES-529 treatment dramatically reduced phosphorylation of AKT at serine 473; however, it did not affect phosphorylation of AKT at threonine 308, suggesting that RES-529 is an inhibitor of mTORC2. Based on its structure, RES-529 is likely not an ATP-competitive inhibitor, 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

…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.

With Phase 1/2 trials set to begin in 2016, we estimate that Phase 3 studies would not begin in either indication until 2018, with an NDA filing likely in 2020 and commercial launch in 2021.

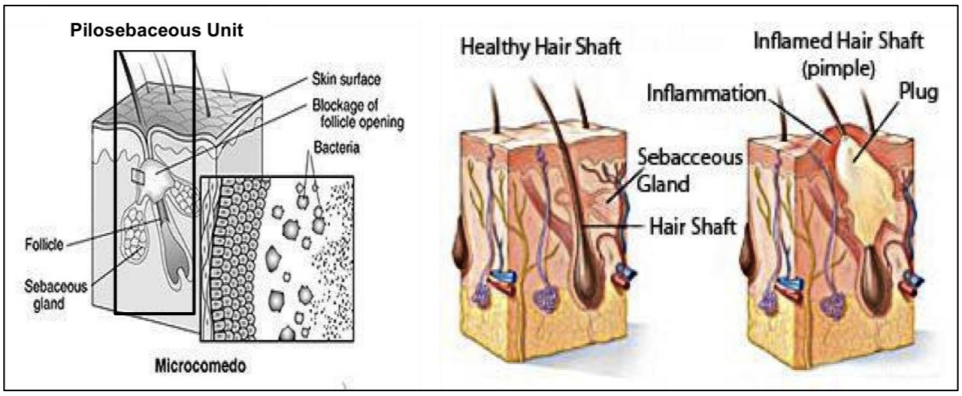
RES-440

In addition to RES-529, RestorGenex is developing RES-440, a first-in-class anti-androgenic compound for the treatment of acne.

…Acne…

Acne vulgaris (or simply acne) is a common skin condition that causes pimples. It can present as non-inflammatory lesions, inflammatory lesions, or a combination of the two. Acne typically affects the face, but can also be found on the chest and back (Dawson *et al*., 2013). It occurs as a result of blockages in the follicles. Excess deposition of keratin, a structural protein that makes up the outer layer of skin, and oily sebum, a substance secreted by the sebaceous gland that helps to keep skin and hair from drying out, results in the formation of a plug, otherwise known as a microcomedo (Benner *et al*., 2013). A microcomedo may go on to form an open comedo ("blackhead") or a closed comedo ("whitehead").

Comedones are associated with the pilosebaceous unit, which includes a hair follicle and a sebaceous gland. These units are found mostly on face, neck, shoulders, chest and upper back (Williams *et al*., 2012). An increase in androgen production causes more sebum to be produced, thus increasing the probability of a plug forming in a hair follicle. After a plug forms, the mostly commensal bacterium *Propionibacterium acnes* can cause inflammation within and around the follicle, leading to inflammatory lesions that causes redness and may lead to scarring or hyperpigmentation.



Source: RestorGenex Corp.

…Current treatment options for acne…

While not a life-threatening condition, severe acne can often impart a substantial psychological burden and negatively impacting a person's quality of life (Barnes *et al*., 2012). Consequently, there is a strong patient-driven demand for effective acne therapies, including prescribed medications and over-the-counter products. As a result, there are a large number of treatments available in a variety of formulations.

Classification of acne according to the severity of lesions into mild (comedones limited to the face), moderate (high number of pustules on the face and mild acne on the body), or severe (nodules and cysts on the face and body) is the first step in treatment, as this will guide the proper therapy. These therapies include topical antibiotics, retinoids, and benzoyl peroxide in monotherapy or in combination products. Systemic medications also include antibiotics and retinoids, as well as hormonal agents, and are only used in patients with moderate to severe acne. For a detailed overview of current treatment recommendation, we refer interested readers to the American Academy of Dermatology treatment guidelines for acne vulgaris.

Topical Therapy

Retinoids have a well-documented history of treating acne effectively. They act by reducing blockages within the follicle and are comedolytic and anti-inflammatory. In addition, they reduce the numbers of microcomedones, comedones, and inflammatory lesions (Gollnick *et al*., 2003). The most commonly prescribed retinoids are adapalene (Differin®), tazarotene (Tazorac®), and tretinoin (Avita®). Several randomized controlled trials have been performed that demonstrated their efficacy and tolerability. In general, all retinoids are effective in reducing the number of comedones and inflammatory lesions by 40-70% (Costa *et al*., 2013).

Antibiotics are mainly used for their role against *P. acnes*, however they may also have anti-inflammatory properties. Unlike retinoids, topical antibiotics are not comedolytic, and their use may lead to antibiotic resistance. Commonly prescribed antibiotics are clindamycin and erythromycin. Topical antibiotics are always used in combination with another treatment, such as a retinoid or benzoyl peroxide.

Benzoyl peroxide is a bactericidal agent and is proven to treat acne. It comes in a variety of prescription and over the counter formulation including soaps, washes, lotions, creams, and gels. Due to its ability to fight antibiotic resistance, these products are typically utilized in conjunction with a topical antibiotic.

Salicylic acid has been used for a number of years to treat acne although there are few clinical trials examining its effectiveness. Its comedolytic properties are less potent than retinoids, thus it is usually prescribed to those individuals who develop skin irritation as a result of topical retinoid treatment.

A number of combination products have also been developed that target multiple pathogenic factors. These include Ziana®, a combination of the antibiotic clindamycin and the retinoid tretinoin, and Epiduo®, a combination of the retinoid adapalene and benzoyl peroxide. These products have been shown to be more effective when compared with using each agent alone (Seidler *et al*., 2011). In addition, combination products have the advantage of simplifying the treatment regimen and reducing the dosing frequency (Alexis, 2008).

Oral Therapy

Oral antibiotics are a common treatment for moderate to severe acne. The tetracycline group of antibiotics is typically prescribed, with doxycycline and minocycline considered to be more effective than tetracycline. Side effects from systemic use of antibiotics include vaginal candidiasis; doxycycline can be associated with photosensitivity; and minocycline has been linked to pigment deposition of the skin, mucus membranes, and teeth.

Hormonal agents have shown some effectiveness in treating acne. Estrogen-containing oral contraceptives have been studied and shown to be effective in treating acne in clinical trials. Spironolactone is an anti-androgen that works by blocking androgen receptors at high concentration, although it may cause hyperkalemia and irregular menstrual periods. Flutamide is a nonsteroidal anti-androgen approved for the management of prostatic hypertrophy and hirsutism, however while effective its use is limited due to the potential for hepatic failure when used systemically.

Isotretinoin, a derivative of vitamin A, has been shown to be the most effective acne treatment, promoting a cure in 85% of cases (Costa *et al*., 2013). However, the drug is associated with a number of severe side effects involving the musculoskeletal, mucocutaneous, and ophthalmic systems. In addition, the drug has been reported to increase the risk for irritable bowel disease, depression, and suicide. Lastly, the compound is a known teratogen, thus females taking the drug must be on a strict pregnancy prevention program. Due to this, the FDA requires all patients taking isotretinoin to sign up with an online tracking database, called iPledge, before receiving their prescription.

…Acne market…

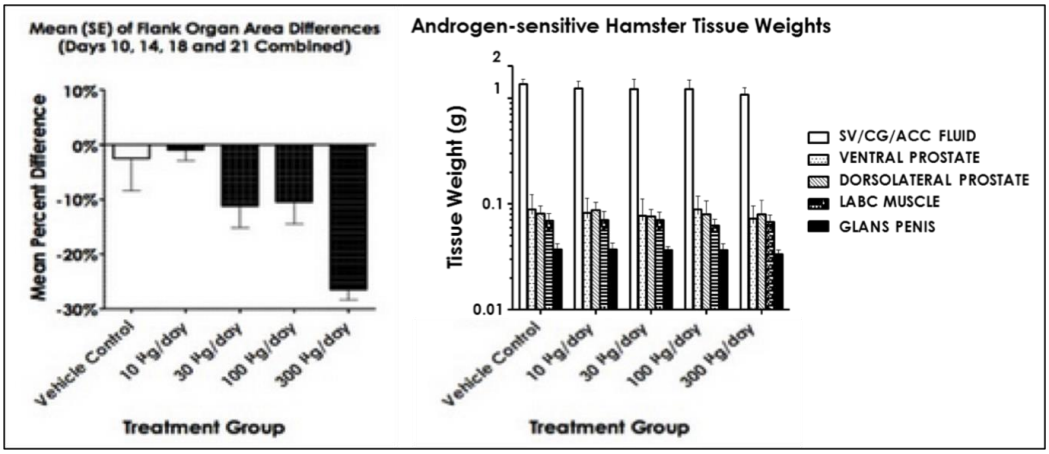
The acne market is divided into over-the-counter (OTC) products and prescription medications. In 2012, according to IMS Health, the top five prescription acne drugs combined for over $1 billion in sales in the U.S. According to IBISWorld Industry Research, the OTC market for acne medications was approximately $2.3 billion in 2012 and was expected to grow to $2.7 billion in 2017. The market is dominated by Johnson & Johnson (Neutrogena, Clean & Clear, Aveeno) and Guthy-Renker (Proactiv), with those companies commanding 29% and 25% of the OTC acne market, respectively.

…RES-440 is a topical anti-androgen with no systemic side effects…

RestorGenex is developing RES-440, which is a carboxylic acid ester of hydroxyflutamide, and is engineered to be the first topical anti-androgen that is rapidly deactivated by hydrolytic enzymes near the site of application to a single inactive metabolite. The company refers to this as a "soft" anti-androgen. The approach has the advantage of sparing internal, androgen sensitive tissues, thus potentially resulting in fewer side effects. The expected major metabolite of RES-440 has no detectable androgen-receptor affinity or ability to interfere with the androgenic effects of endogenous androgens.

The Syrian Golden Hamster model has long been validated as a model for topical anti-androgens as the animals have flank glands that are highly sensitive to androgen stimulation. The sebaceous gland flank organ spots are visible as a dark raised spot on each flank. Application of anti-androgenic compounds will cause the glands to diminish in size. The advantage of this model is that one gland can be treated with the test compound and the other compound with a control.

Topical doses of RES-440 from 10 to 300 µg/day were administered to male Golden Syrian Hamsters. In addition to monitoring the untreated flank organ size for systemic effects, androgen-sensitive tissues collected at the end of the experiment were weighed and compared to vehicle-treated intact animals and castrated controls. The results of the Golden Syrian Hamster study with RES-440 are shown below.



Source: RestorGenex Corp.

The above left figure shows the result of treating the hind flank glands with the indicated amount of RES-440 once-daily for 21 days. The data show that the gland treated with 300 µg per day was almost 30% smaller than the flank treated with vehicle control. In addition, there did not appear to be any affect on various androgen sensitive tissues, as shown by the above right figure. Taken together, these data indicate that RES-440 has potent anti-androgenic activity that is locally contained and does not result in systemic effects.

…RES-440 development plan…

RES-440 has a number of advantages over currently available acne therapeutics including a short half-life, an inactive metabolite (to avoid systemic side effects), a melting point very near body temperature making it possible to penetrate into the pilosebaceous unit, and its stable at skin pH.

RestorGenex is planning to complete preclinical and toxicology studies to enable an Investigational New Drug (IND) application to be filed in 2016. The company will then initiate Phase 1/2 clinical trials to study the safety and efficacy of RES-440. Differin® was approved with a single 12-week study involving 653 patients, thus RestorGenex could potentially be ready to perform a Phase 3 study in 2017 and file the U.S. NDA in 2018. If all goes well, RES-440 could be ready for commercial launch in 2019.

Financial Position

As of December 31, 2014, RestorGenex was well capitalized, with approximately $20 million in cash and cash equivalents and no debt. We view this as sufficient to fund operations through the end of 2015 and into 2016. In addition, the company has approximately 4.8 million warrants outstanding, with most expiring in Q2 2018 with a $4.80 exercise price. Thus, there is the potential for an additional influx of $23 million in cash from those warrants.

MANAGEMENT PROFILES

Stephen M. Simes – Chief Executive Officer

Mr. Simes is the Chief Executive Officer of RestorGenex. Mr. Simes served as Vice Chairman, President, Chief Executive Officer, and a director of BioSante Pharmaceuticals, Inc. from 1998 until June 19, 2013 when BioSante merged with ANIP Acquisition Company, d/b/a ANI Pharmaceuticals, Inc. BioSante, whose stock was listed on The NASDAQ Global Markets, was a specialty pharmaceutical company focused on developing products for women's and men's health and oncology. From 1994 to 1997, Mr. Simes was President, Chief Executive Officer, and a Director of Unimed Pharmaceuticals, Inc., (currently a wholly owned subsidiary of AbbVie, Inc.) a company with a product focus on infectious diseases, AIDS, endocrinology, and oncology. From 1989 to 1993, Mr. Simes was Chairman, President, and Chief Executive Officer of Gynex Pharmaceuticals, Inc., a company that concentrated on the AIDS, endocrinology, urology, and growth disorders markets. In 1993, Gynex was acquired by Savient Pharmaceuticals Inc. (formerly Bio-Technology General Corp.), and from 1993 to 1994, Mr. Simes served as Senior Vice President and director of Savient Pharmaceuticals Inc. Mr. Simes' career in the pharmaceutical industry started in 1974 with G.D. Searle & Co. (now a part of Pfizer Inc.). Mr. Simes earned his MBA in Marketing and Finance from New York University, having earlier received a Bachelor of Science degree in Chemistry at Brooklyn College of the City University of New York.

Phillip Donenberg – Chief Financial Officer and Secretary

Mr. Donenberg is the Chief Financial Officer and Secretary of RestorGenex. Mr. Donenberg previously served as BioSante Pharmaceuticals, Inc.'s Senior Vice President of Finance from 2010 until June 19, 2013 and Chief Financial Officer and Secretary from 1998 until June 19, 2013 when BioSante merged with ANIP Acquisition Company, d/b/a ANI Pharmaceuticals, Inc. BioSante, whose stock was listed on the NASDAQ Global Markets, was a specialty pharmaceutical company focused on developing products for women's and men's health and oncology. From 1995 to 1998, Mr. Donenberg was Controller of Unimed Pharmaceuticals, Inc. (currently a wholly owned subsidiary of AbbVie Inc.), a company with a product focus on infectious diseases, AIDS, endocrinology, and oncology. Prior to Unimed Pharmaceuticals, Inc., Mr. Donenberg held similar positions with several other pharmaceutical companies. Mr. Donenberg earned his BS in Accountancy from the University of Illinois Champaign-Urbana, College of Business and is a Certified Public Accountant.

Mark Weinberg, MD – Senior Vice President – Clinical Development

Dr. Weinberg has served as Senior Vice President of Clinical Development since August 2014. Dr. Weinberg joined RestorGenex from Astellas Pharma Global Development where he served as Vice President, Global Clinical Science from June 2013 to August 2014 and had also served as the Global Therapeutic Area Head, CNS and Pain from April 2011 to June 2013. Prior to Astellas, he held several roles at Lundbeck Inc. (formerly Ovation Pharmaceuticals) from July 2008 to April 2011. These included Vice President, Medical Strategy, Vice President, Medical Affairs, and Vice President, Clinical Research. Prior to joining Ovation Pharmaceuticals in 2011, Dr. Weinberg held roles of increasing responsibility in clinical development at Takeda Global Research and Development and Abbott Laboratories. He has worked in several therapeutic areas during his career including oncology, CNS, pain, hematology, ophthalmology, rheumatology, and dermatology with activities spanning Phase 1 through 4 and regulatory interactions on INDs, SPAs, and NDAs. Dr. Weinberg earned his M.D. from Duke University Medical School and remained there to complete a residency in internal medicine. He also holds an MBA from the Kellogg Business School of Northwestern University and a BA in economics from Yale University.

VALUATION AND RECOMMENDATION

We are initiating coverage of RestorGenex Corp. (RESX) with an Outperform rating and a price target of $6.50.

RestorGenex 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. RES-529 has completed two Phase 1 trials in Age-Related Macular Degeneration (AMD) and a number of preclinical studies supporting the drug's use in the treatment of glioblastoma multiforme (GBM). RES-440 is a first-in-class "soft" anti-androgen for the treatment of acne vulgaris, or simply acne. The drug is designed to be a potent anti-androgen while being rapidly metabolized locally to an inactive metabolite, thus decreasing any potential adverse systemic effects that are common with other anti-androgen therapies.

…RES-529 Targets the PI3K Signaling Pathway…

The phosphatidylinositol 3-kinase (PI3K) pathway is a key signal transduction system that links multiple cell receptors to many essential cellular functions and 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. Preclinical studies showed that RES-529 is an inhibitor of the mTORC1 and mTORC2 complexes, both of which are involved in signal propagation in the PI3K pathway. Inhibition of one or the other complexes has shown limited efficacy in clinical testing, thus a compound that targets both complexes is likely to completely shut down the pathway and result in an enhanced therapeutic effect.

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 expression is increased through activation of the PI3K signaling pathway, thus inhibition of PI3K signaling can have a direct effect on angiogenesis.

…One Compound, Two Indications…

RES-529 is being developed as a treatment for both wet age related macular degeneration (wet AMD) and glioblastoma multiforme (GBM), two indications that rely upon improper PI3K signaling and pathologic activation of angiogenesis. Wet AMD involves the abnormal growth of blood vessels (angiogenesis) behind the retina under the macula due to increased expression of 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, resulting in loss of central vision very quickly.

GBM is a grade IV brain tumor characterized by a heterogeneous cell population with a number of negative attributes, including the increased expression of VEGF. The prognosis for patients diagnosed with GBM is quite grim, with a median overall survival time of only 15 months. Based on the difficulties in therapeutic development, the limited treatment options, the grim prognosis for GBM patients, and resistance mechanisms intrinsic to GBM, there is a significant unmet medical need for more efficacious GBM therapies.

…RES-440 Could Differentiate Itself in Crowded Acne Market…

There are a number of acne medications currently available, both over the counter and by prescription, thus in order to gain appreciable market share it is necessary for any potential acne therapeutic to clearly differentiate itself. RES-440 is unique among anti-androgens in that it is rapidly deactivated by hydrolytic enzymes near the site of application to a single inactive metabolite. The company refers to this as a "soft" anti-androgen. The approach has the advantage of sparing internal, androgen sensitive tissues, thus potentially resulting in fewer side effects. The expected major metabolite of RES-440 has no detectable androgen-receptor affinity or ability to interfere with the androgenic effects of endogenous androgens.

…Early in Development, But With Large Upside Potential…

RestorGenex will be finalizing the CMC work of the active pharmaceutical ingredient (API) for RES-529 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. RES-529 has already been studied in two Phase 1 clinical trials for wet AMD. A total of 20 wet AMD patients were treated, with no serious adverse events reported. 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. 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, 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.

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.

For both indications, with Phase 1/2 trials set to begin in 2016, we estimate that Phase 3 studies would not begin until 2018, with an NDA filing likely in 2020 and commercial launch in 2021.

RestorGenex is planning to complete preclinical and toxicology studies of RES-440 to enable an IND application to be filed in 2016. The company will then initiate Phase 1/2 clinical trials to study the safety and efficacy of RES-440. Differin® was approved with a single 12-week study involving 653 patients, thus RestorGenex could potentially be ready to perform a Phase 3 study in 2017 and file the U.S. NDA in 2018. If all goes well, RES-440 could be ready for commercial launch in 2019.

RestorGenex currently has a market cap of approximately $76 million on a fully diluted basis. The company currently has approximately $20 million in cash and cash equivalents, thus there is plenty of capital to get the requisite IND enabling studies completed as well as initiate the Phase 1/2 clinical trials. The company is targeting three multi-billion dollar indications. 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 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. This gives an estimated net present value for each indication of $125 million for wet AMD, $23.6 million for GBM, and $32.2 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 $176. Dividing this total by the fully diluted share count of 27.1 million shares leads to a fair value of approximately $6.50 and we are assigning an 'Outperform' rating to the stock.

PROJECTED FINANCIALS

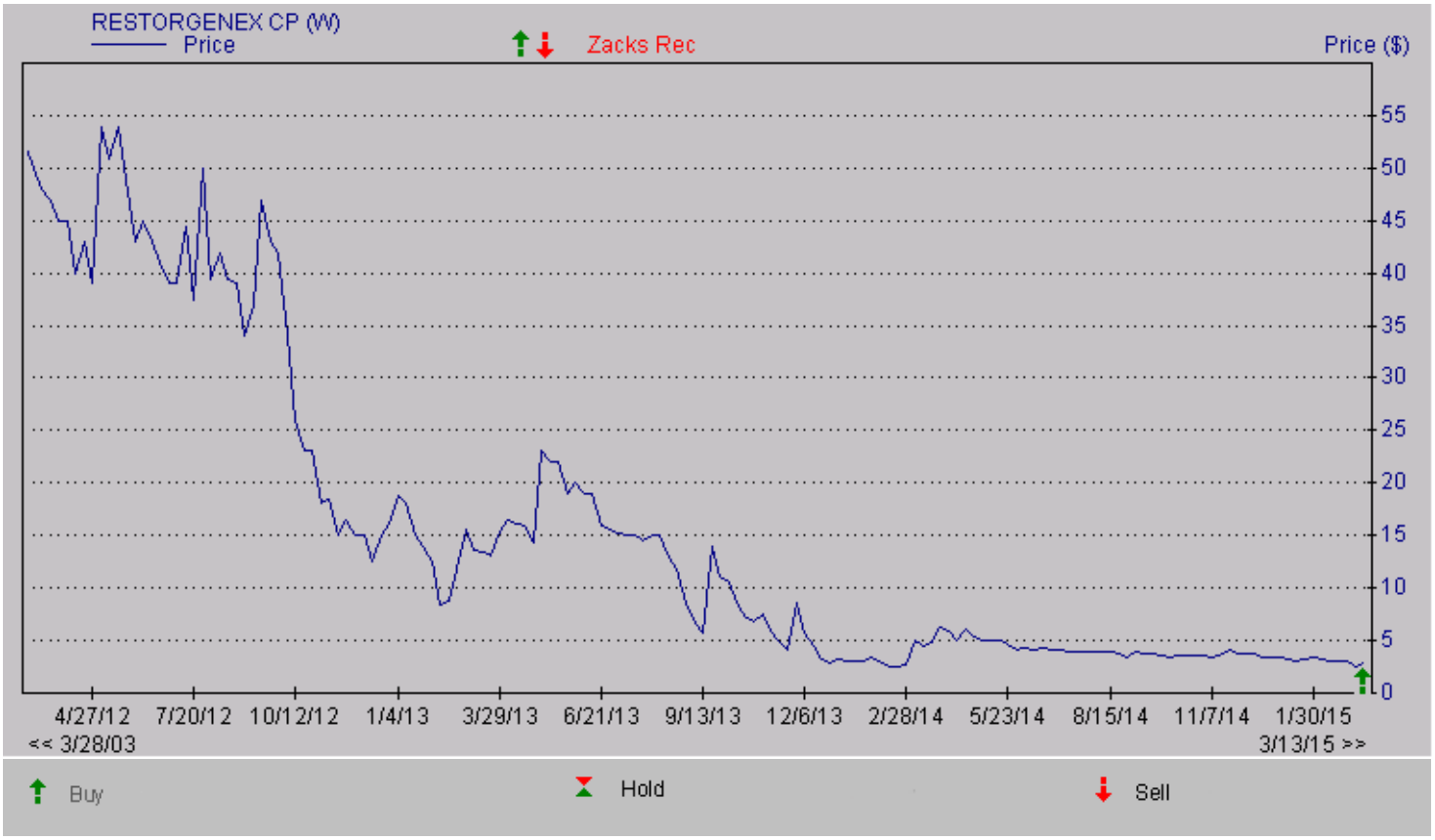
RestorGenex Corp.
Income Statement

RextorGenex Corp.	2013 A	Q1 A	Q2 A	Q3 A	Q4 E	2014 E	2015 E	2016 E
RES-529 (Wet AMD)	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-
RES-529 (Oncology)	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-
RES-440 (Acne)	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-
Grants & Collaborative Revenue	$0	$0	$0	$0	$0	$0	$0	$0
YOY Growth	-	-	-	-	-	-	-	-
Total Revenues	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**	**$0**
YOY Growth	-	-	-	-	-	-	-	-
Cost of Sales	$0	$0	$0	$0	$0	$0	$0	$0
Product Gross Margin	-	-	-	-	-	-	-	-
Research & Development	$1.0	$0.0	$0.4	$0.9	$1.0	$2.3	$3.5	$6.0
General & Administrative	$1.0	$0.6	$0.3	$0.8	$0.9	$2.6	$3.3	$5.0
Other Expenses	$11.0	$0.8	$3.8	$1.7	$1.5	$7.8	$3.0	$2.5
Operating Income	($12.9)	($1.4)	($4.5)	($3.5)	($3.4)	($12.8)	($9.80)	($13.50)
Operating Margin	-	-	-	-	-	-	-	-
Non-Operating Expenses (Net)	$10.459	($0.009)	$0.052	$0.062	($0.500)	($0.4)	($0.1)	($0.1)
Preferred Dividends	$0.172	$0.000	$0.000	$0.000	$0.000	$0.0	$0.0	$0.0
Pre-Tax Income	($2.6)	($1.4)	($4.5)	($3.4)	($3.9)	($13.2)	($9.9)	($13.6)
Net loss attributed to non-controlling interest	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Income Taxes Paid	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Tax Rate	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*	*0%*
Net Income	**($2.6)**	**($1.4)**	**($4.5)**	**($3.4)**	**($3.9)**	**($13.2)**	**($9.9)**	**($13.6)**
Net Margin	-	-	-	-	-	-	-	-
Reported EPS	**($1.00)**	**($0.23)**	**($0.35)**	**($0.18)**	**($0.19)**	**($0.91)**	**($0.37)**	**($0.41)**
YOY Growth	-	-	-	-	-	-	-	-
Basic Shares Outstanding	2.647	5.934	12.868	18.671	20.200	14.418	27.000	33.000

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

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Sell/Underperform: The analyst expects the company will underperform the broader U.S. Equity market over the next one to two quarters.

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