Rexahn Pharmaceuticals (RNN)

Initiation Report

LifeSci Investment Abstract

Rexahn (NYSE MKT: RNN) is a biopharmaceutical company developing targeted therapeutics for solid tumors. Three candidates are in clinical trials and results are expected from each program in the next 12 months. Archexin is an antisense oligonucleotide targeting AKT1 that is being tested in a randomized Phase IIa trial for renal cell carcinoma (RCC). RX-3117 is a next-generation oral anti-metabolite with broad anti-cancer activity, and is being evaluated in a Phase Ib/IIa study. Supinoxin is an oral inhibitor of phosphorylated p68, a novel oncology target, and is expected to enter a Phase Ib/IIa trial in the third quarter of 2016.

Key Points of Discussion

- **Rexahn is Developing Targeted Cancer Therapeutics.** Rexahn has 3 clinical programs in development for cancer patients, and each candidate either targets a cancer-specific protein or is predominately activated in cancer cells. Archexin is an antisense oligonucleotide that blocks AKT1 translation, RX-3117 is a cytotoxic anti-metabolite activated by uridine-cytidine kinase 2 (UCK2), and Supinoxin inhibits phosphorylated p68. The targeted strategy featured in these candidates has the potential to minimize off-target side effects typically observed with chemotherapy. It also provides an opportunity for upfront patient selection in clinical trials using biomarkers, which can improve the chances of success.

- **Lead Candidate Archexin is in a Randomized Phase IIa Trial for Renal Cell Carcinoma.** Rexahn is examining Archexin in a Phase I/IIa trial for the treatment of metastatic RCC patients who failed a prior VEGF inhibitor. The maximum tolerated dose of Archexin was established in Phase I and initial signals of activity were observed. Stable disease was observed in 40% (4/10) of evaluable patients. The median duration of stable disease was 183.5 days. Three of these patients had reductions in tumor size of 16%, 32%, and 36% that did not meet RECIST criteria for tumor response, but we consider as contributing evidence of Archexin's potential efficacy, especially considering that single lesion responses were observed.

Expected Upcoming Milestones

- Q2/Q3 2016 – Complete Phase I study with Supinoxin and establish recommended Phase II dose.
- Q3 2016 – Initiate Phase Ib/IIa trial with Supinoxin in triple negative breast cancer (TNBC) and relapsed advanced ovarian cancer patients.
- H2 2016 – Interim data from Phase Ib/IIa study with RX-3117 in pancreatic cancer and bladder cancer patients.
- 2016 – Present full data from Phase Ib trial with RX-3117 in advanced cancer patients.
- Late 2016/Early 2017 – Interim data from Phase Ib/IIa study with Supinoxin in TNBC and relapsed advanced ovarian cancer patients.
- H1 2017 – Results from randomized Phase IIa trial with Archexin in renal cell carcinoma patients.

Market Data

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<th>Net Cash/Share</th>
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Financials

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</table>

For analyst certification and disclosures please see page 42
The Phase IIa portion of the trial is enrolling patients who are randomized 2:1 to receive Archexin plus Afinitor or Afinitor monotherapy. Full results are expected in the first half of 2017 and could be presented at AACR or ASCO 2017. Since the trial is open-label, initial data could be reported earlier.

- **Multiple Clinical Catalysts Expected in the Next 12 Months.** Over the next year, Rexahn is expected to release data from 3 clinical trials across 5 disease indications. The first results are expected in the second half of 2016 from a Phase Ib/IIa trial with RX-3117 in pancreatic cancer and bladder cancer patients. Additional data will be presented between late 2016 and the first half of 2017 from the two other programs, including randomized Phase IIa data with lead candidate Archexin in patients with RCC.

- **RX-3117 Could Address a Broad Range of Cancers.** RX-3117 is a cytotoxic anti-metabolite that is activated by uridine-cytidine kinase 2 (UCK2), an enzyme overexpressed in several forms of cancer but minimally present in normal tissues. It is being developed as a treatment for multiple types of cancer, and preclinical studies have indicated that RX-3117 has activity in gemcitabine resistant cells. This feature is important since gemcitabine is used to treat many types of cancers, and Rexahn estimates that 25-40% of these individuals will become resistant.

Rexahn has identified a maximum tolerated dose of RX-3117 and in March launched a Phase Ib/IIa study that is currently enrolling patients with relapsed or refractory pancreatic cancer and advanced bladder cancer. The primary endpoints of the study are progression free survival (PFS), objective clinical response rate, and reduction in tumor size. Interim results are expected in the second half of 2016. The true timing of initial data depends on the results from patients in part 1 of the study. For example, based on the two stage design, if the first few patients experience tumor responses or extended progression free survival, Rexahn could trigger the enrollment of additional patients in part 2 and disclose the activity from part 1. Otherwise, we expect that the 2016 European Society for Medical Oncology (ESMO) is a possible venue for presentation of initial Phase Ib/IIa data.

- **Supinoxin Inhibits Novel Target that Could Enable Patient Selection.** Supinoxin is a highly potent, orally available inhibitor of phosphorylated p68 (phospho-p68), a unique target that appears to be exclusively expressed in cancer cells. We are unaware of any clinical programs targeting phospho-p68 other than Supinoxin. Inhibition of phospho-p68 disrupts aberrant signaling through the well-characterized Wnt/β-catenin signaling pathway, but in a Wnt independent fashion. This leads to inhibition of cell proliferation and migration.

Rexahn is currently conducting a Phase I trial with Supinoxin and presented interim clinical data at the 2015 European Cancer Congress (ECC) showing a favorable safety profile and indications of preliminary clinical activity. The Company is planning to launch a Phase Ib/IIa trial in the third quarter of 2016 that will enroll patients with triple negative breast cancer and relapsed advanced ovarian cancer. Interim data from the Phase Ib/IIa are expected in late 2016 or early 2017.

- **Five Initial Target Indications Represent Significant Market Opportunity.** Between Rexahn’s 3 clinical programs, the Company is targeting 5 disease indications with a large total market opportunity. We estimate that the addressable population exceeds 100,000 patients per year in the US. We also estimate that lead candidate Archexin could generate between $175 to $524 million in peak annual revenues in renal cell carcinoma. There are very few treatment options for the remaining indications, which include pancreatic cancer, bladder cancer, triple-negative breast cancer, and relapsed advanced ovarian cancer, suggesting that doctors and patients will be highly motivated to use newly approved therapies.
Financial Discussion

Financial Results for the First Quarter of 2016. On May 9, 2016, Rexahn announced first quarter 2016 financial results. The Company had a net loss of $4.1 million, or ($0.02) per share for the first quarter of 2016 compared to a net loss of $4.3 million, or ($0.2) per share for first quarter of 2015. Research and development costs totaled $3.5 million for the first quarter of 2016 compared to $2.9 million for same period of 2015. This increase is mainly due to additional clinical trial and drug manufacturing costs related to Supinoxin and Archexin. General and administrative expenses total $1.4 million for the 3 months ended March 31, 2016 compared to $1.5 million for first quarter of 2015. As of March 31, 2016, the Company had cash, cash equivalents, and marketable securities of $24.5 million, which is estimated to fund activities into the second half of 2017. On March 2, 2016, Rexahn completed a registered direct offering of common stock and warrants for net proceeds of $4.6 million.
# Table of Contents

- Company Description .................................................................................................................. 5
- Archexin: Oligonucleotide Inhibitor of AKT1 .............................................................................. 6
  - Mechanism of Action .................................................................................................................. 6
  - Preclinical Studies with Archexin .............................................................................................. 9
- Metastatic Renal Cell Carcinoma .................................................................................................. 10
  - Renal Cell Carcinoma – Market Information .......................................................................... 12
- Clinical Data Discussion for Archexin .......................................................................................... 14
  - Phase IIa Trial in Metastatic Pancreatic Cancer Patients ........................................................... 14
  - Phase I/IIa Trial in Metastatic Renal Cell Carcinoma ............................................................... 15
- Competitive Landscape for RCC .................................................................................................. 17
- RX-3117: Oral Next-Generation Nucleoside Analogue ................................................................. 18
  - Mechanism of Action ................................................................................................................ 19
  - Preclinical Studies with RX-3117 .............................................................................................. 21
- Target Indications for RX-3117 .................................................................................................... 24
  - Pancreatic Cancer ..................................................................................................................... 24
  - Bladder Cancer .......................................................................................................................... 25
- Market for Pancreatic and Bladder Cancer .................................................................................... 26
- Clinical Data Discussion for RX-3117 .......................................................................................... 27
- Supinoxin (RX-5002): Phosphorylated p68 Inhibitor .................................................................. 28
  - Mechanism of Action ................................................................................................................ 29
  - Supinoxin Preclinical Studies ..................................................................................................... 31
- Target Indications for Supinoxin .................................................................................................... 33
  - Triple Negative Breast Cancer .................................................................................................... 33
  - Ovarian Cancer ........................................................................................................................... 35
- Market Estimate for TNBC and Advanced Ovarian Cancer ......................................................... 36
- Clinical Data Discussion for Supinoxin .......................................................................................... 38
  - Ongoing Phase I Clinical Trial with Supinoxin in Cancer Patients ............................................. 38
    - Planned Phase Ib/IIa Study ......................................................................................................... 39
- Intellectual Property & Licensing ............................................................................................... 39
- Management Team ...................................................................................................................... 40
- Risk to an Investment .................................................................................................................... 41
- Analyst Certification ..................................................................................................................... 42
- Disclosures ................................................................................................................................... 42
Company Description

Rexahn Pharmaceuticals is developing therapeutics for difficult to treat cancers. The Company’s lead candidate, Archexin, is an antisense oligonucleotide that is specific for the Akt1 gene and reduces signaling through the PI3K/AKT1/mTOR pathway. It is currently being evaluated in a Phase IIa study in combination with Afinitor (everolimus) as a second line treatment for renal cell carcinoma. Results from the dose-escalating portion of this study showed a tumor reduction in 3 patients of 16%, 36%, and 32% when treated with 125, 200, and 250 mg/m²/day of Archexin and Afinitor, respectively. The Stage 2 portion of this study will randomize 30 patients to receive either Archexin in combination with Afinitor, or Afinitor alone. Rexahn’s full developmental pipeline is illustrated in Figure 1.

**Figure 1. Rexahn’s Developmental Pipeline**

<table>
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<th></th>
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<th>Phase Ib/IIa</th>
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Source: LifeSci Capital

Rexahn is developing RX-3117 as a treatment for patients with pancreatic and bladder cancer. RX-3117 is an orally administered cytotoxic anti-metabolite that differs from gemcitabine by being activated by uridine-cytidine kinase 2 (UCK2), instead of deoxycytidine kinase (dCK). Down regulation of dCK often leads to resistance in gemcitabine resistant cancers, and RX-3117 may provide an alternative treatment for these patients. Preclinical studies suggest that RX-3117 may have broad activity in cancer, and it is currently being evaluated in Phase Ib/IIa study in pancreatic cancer and bladder cancer patients that commenced in March 2016. Interim data from the study are expected in the second half of 2016.

Supinoxin (RX-5902) is an inhibitor of phosphorylated p68. It is the only clinical program addressing this target to our knowledge. Supinoxin is currently being evaluated in a Phase I study in patients with relapsed and refractory solid tumors, and study completion is expected in the second or third quarter of 2016. The Company also plans to initiate a Phase Ib/IIa trial in the third quarter 2016. The trial will enroll patients with triple negative breast cancer and relapsed advanced ovarian cancer. Interim data from the Phase Ib/IIa study are expected in late 2016 or early 2017.
Archexin: Oligonucleotide Inhibitor of AKT1

Archexin is an intravenously administered antisense oligonucleotide in development as a potential treatment for metastatic renal cell carcinoma (RCC). It is complementary to AKT1 mRNA, and leads to reduced protein expression of this important signaling protein. AKT1 is one of three AKT isoforms: AKT1, AKT2, and AKT3. It is generally associated with enhanced cell proliferation and survival, and inhibition of apoptosis.1 AKT overexpression has been observed in several cancers, including renal cell, gastric, breast, ovarian, and prostate.2,3 The sequence of Archexin, which is a 20 base pair long (20-mer) oligonucleotide, is shown in Figure 2. Inhibiting AKT1 signaling induces apoptosis and reduces the growth of tumor cells that are dependent on this pathway for survival.4 Archexin is currently being evaluated in a Phase Ib/IIa study in combination with Afinitor to treat metastatic RCC. Interim Phase Ib results were presented at the 2016 American Association for Cancer Research (AACR) showing evidence of anti-tumor activity.

**Figure 2. Molecular Sequence of Archexin**

5'-G-C-T-G-C-A-T-G-A-T-C-T-C-T-C-T-G-G-C-G-3'

Source: LifeSci Capital

**Mechanism of Action**

Archexin is a first-generation, 20-mer, antisense oligonucleotide (ASO) that binds AKT1 mRNA to inhibit AKT1 protein production. As shown in Figure 3, ASOs have sequence complementarity to the mRNA of a gene of interest. They form an RNA-ASO double helix when bound to the target mRNA, and this interaction triggers transcript cleavage to prevent protein translation.

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Archexin is able to reduce protein levels of both native and activated AKT1, since activation occurs at the protein level. We believe this may be a more robust mechanism for blocking AKT signaling than other approaches such as inhibition of the PI3K protein, which is an upstream component of the pathway. Inhibition of PI3K only partially blocks the activation and downstream signaling of AKT1, since there are multiple inputs that can activate AKT1. In the case of PI3K inhibition, unphosphorylated AKT1 is still present and capable of activation via other upstream signals. Archexin decreases total AKT protein levels and minimizes activation from all sources.

**AKT1 Background.** AKT is part of the PI3K-AKT-mTOR signal transduction pathway that promotes cell survival, proliferation, cell migration, and angiogenesis through the phosphorylation of multiple substrates.\(^5\) One of the main negative regulators of this pathway is the phosphate and tensin homolog (PTEN) protein, which inhibits signaling by dephosphorylating AKT. Mutations of the PTEN gene have been associated with the development of several cancers, including renal cell carcinoma.\(^6\) In addition, AKT activation has been associated with chemoresistance.\(^7\) AKT1 is one of three AKT isoforms: AKT1 (PKBα), AKT2 (PKBβ), and AKT3 (PKBγ). As shown in Figure 4, each plays a different role in cellular survival and proliferation.\(^8\)

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Figure 4. Elucidation of the Physiological Roles of AKT Isoforms Through Gene Ablation in Mice

<table>
<thead>
<tr>
<th>Isoform</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKT1</td>
<td>Placental development, animal growth, and adipogenesis</td>
</tr>
<tr>
<td>AKT2</td>
<td>Glucose metabolism, animal growth, adipogenesis, and maintenance</td>
</tr>
<tr>
<td>AKT3</td>
<td>Postnatal brain growth</td>
</tr>
</tbody>
</table>

Source: LifeSci Capital

Approved Cancer Therapeutics for the AKT Pathway. As shown in Figure 5, AKT is a component of several signaling cascades that impact cell survival, angiogenesis, and cell-cycle control. Signaling cascades transmit information from cell membrane receptors to transcription factors that influence gene transcription. There are often several proteins that comprise the signaling chain and some are good drug targets. Several drugs have received approval that target proteins in AKT-related signaling pathways, such as Novartis’ (NYSE: NVS) Afinitor (everolimus) and Pfizer’s (NYSE: PFE) Torisel (temsirolimus) for mTOR, and Roche’s (VTX: ROG.VX) Avastin (bevacizumab) and Amgen’s (NasdaqGS: AMGN) Nexavar (sorafenib) for VEGF.

Figure 5. AKT Signaling Pathway

Source: Company Presentation

There are currently no drugs approved that target AKT. Some AKT inhibitors were previously in development as treatments for cancer, but were discontinued due to safety, undesirable pharmacokinetics, and inferiority reasons. Notably, none of these agents were oligonucleotides, none specifically targeted the AKT1 isomer, and none were able to reduce levels of phosphorylated and unphosphorylated AKT1. Archexin, on the other hand, primarily disrupts AKT1 synthesis and may be more tolerable due to this specificity. Rexahn is evaluating Archexin in combination with Afinitor, which may act synergistically with each other to prevent cancer cell growth and proliferation.
History of Antisense Drugs. Two antisense products have been approved by the FDA. Both were developed by Ionis Pharmaceuticals (NasdaqGS: IONS), which is a company that is primarily focused on the creation of new RNA-targeted therapeutics. Kynamro (mipomersen) was approved in 2013 as a treatment for homozygous familial hypercholesterolemia (HoFH). Because of toxicity issues pertaining to an increase in liver fat and elevated transaminases, Kynamro is only available through a restricted prescribing and distribution program. The other agent, Vitravene (fomivirsen), was approved in 1998 for the treatment of cytomegalovirus (CMV) retinitis in patients with AIDS. Improved treatment outcomes for patients with HIV have significantly decreased the incidence of CMV retinitis, and Vitravene was withdrawn from the US market in 2006 as a result of declining sales. Therefore, we acknowledge that historically there have been challenges with antisense drug development and commercialization, some related to the technology and some due to uncontrollable disease dynamics.

Despite these challenges, there are more than 45 antisense agents in clinical development for several therapeutic areas including cancer. It indicates that there is still optimism surrounding this treatment approach. Rexahn is the only company with an antisense oligonucleotide in development for RCC that targets AKT1 mRNA. Because there are three isoforms of the AKT receptor, antisense seems to be the best approach to selectively target AKT1 without also reducing levels of AKT2 and AKT3. Previous drugs that have been developed to target AKT were unable to differentiate between the three isomers, and were ultimately discontinued due to safety, PK, and inferiority reasons.

Preclinical Studies with Archexin

Anti-Tumor Activity of Archexin in an Animal Model of Pancreatic Cancer. Archexin was analyzed in a mouse model of pancreatic cancer to explore its preclinical efficacy. Nude mice were subcutaneously implanted with $2.5 \times 10^6$ human pancreatic cancer cells. The cell line is called MIA due to the expression of melanoma inhibitory activity (MIA), which is a secreted protein that increases the invasiveness of the cells. They also contained a luciferase protein that allowed them to be monitored through imaging. Two weeks following implantation, the mice were treated with 30 mg/kg of continuously infused Archexin for a two-week period.

Figure 6 shows tumor reduction following treatment with Archexin over this time. The coloring in the picture represents the cancer cells, since they express the light-producing luciferase protein. An approximation of the number of cancer cells is shown in lower left side of each of the 4 panels. The top left panel shows the mice at 1 week following cancer cell implantation, and the top right panel is 2 weeks after implantation. As expected, the cancer grows between week 1 and week 2. The lower left panel is 1 week following Archexin treatment, and the lower right panel is 2 weeks following treatment. Archexin treatment led to a full eradication of the cancer cells after 2 weeks as measured by the luciferase-based imaging. The data indicate that Archexin has anti-tumor activity, supporting its clinical development.

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Figure 6. Anti-Tumor Activity of Archexin

Safety Profile. Archexin has been evaluated in a Phase I study in solid tumors, and a small Phase IIa trial in advanced pancreatic cancer patients. Treatment was overall safe and well tolerated. The dose limiting toxicity was Grade 3 fatigue, and the most frequently reported adverse events included fatigue, nausea, anorexia, and joint pain. There was an absence of AEs commonly reported with inhibitors of this pathway such as rash and hypoglycemia.

Metastatic Renal Cell Carcinoma

Renal cell carcinoma (RCC) is a form of cancer that develops in the tubules of the kidneys. It is the most common type of kidney cancer and represents 90% of cases. The 5-year survival rate for patients with metastatic disease is approximately 12%.

RCC is divided into several types based on histological features. Figure 7 shows the 5 most common forms and their prevalence. Clear cell is the most common RCC type and represents approximately 70% of cases.
Figure 7. Renal Cell Carcinoma Types

<table>
<thead>
<tr>
<th>Renal Cell Carcinoma Type</th>
<th>Prevalence</th>
<th>Feature</th>
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<tr>
<td>Clear cell</td>
<td>70%</td>
<td>Can grow both slow and fast, responds well to treatment</td>
</tr>
<tr>
<td>Papillary</td>
<td>15%</td>
<td>Not as responsive as clear cell, finger-like appearance</td>
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<tr>
<td>Chromophobe</td>
<td>5-10%</td>
<td>Less aggressive growth, large in size</td>
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<tr>
<td>Oncocytoma</td>
<td>5%</td>
<td>Usually benign, large in size</td>
</tr>
<tr>
<td>Collecting duct</td>
<td>&lt;1%</td>
<td>Aggressive growth, irregular tube appearance</td>
</tr>
</tbody>
</table>

Source: American Cancer Society

Symptoms of RCC vary based on the stage of cancer. Early-stage patients often exhibit a triad of symptoms such as blood in the urine, a mass on the flank, and flank pain. As the disease worsens, patients may experience anemia, high blood pressure, and high calcium levels in the blood. According to a physician at MD Anderson, 25-33% of RCC patients have metastatic disease when they are first diagnosed, and 20-40% of individuals who start treatment for a localized tumor will become metastatic. RCC is generally detected through lab tests, CAT scan, MRI, and biopsy. Known risk factors associated with RCC include the following:

- Smoking.
- High BMI.
- Hypertension.
- Kidney disease.
- Being a male.
- Genetic factors.

Renal Cell Carcinoma Standard of Care. RCC treatment has changed dramatically over the last several years due to earlier detection, less invasive surgeries, and the approval of several systemic agents for advanced disease. For early-stage RCC patients, surgical resection by partial or radical nephrectomy is the typical plan of action. Not all patients are considered good candidates for surgery and receive other treatments such as radiation therapy, cryotherapy, arterial embolization, and radiofrequency ablation. It is worth noting that chemotherapy usually does not incite a successful response, and is rarely used as a form of treatment. Late-stage RCC patients often undergo a nephrectomy and may receive cytokine therapy such as high-dose IL-2, or a targeted therapy like a VEGF-, mTOR-, or PD-1 inhibitor. IL-2 therapy is highly toxic and difficult to administer, so only a small percentage of patients are eligible to receive this treatment. The FDA-approved first and second line therapies are shown in Figure 8.

10 http://www2.mdanderson.org/depts/oncolog/articles/12/5-may/5-12-compass.html
11 http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/nephrology/renal-cell-carcinoma/#s0035
13 http://www2.mdanderson.org/depts/oncolog/articles/12/5-may/5-12-compass.html
## Figure 8. Approved Treatments for Renal Cell Carcinoma

<table>
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<th>Drug</th>
<th>Company</th>
<th>Mechanism</th>
<th>Line of Therapy</th>
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</thead>
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<tr>
<td>Torisel (temsirolimus)</td>
<td>Pfizer (NYSE: PFE)</td>
<td>mTOR inhibitor</td>
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</tr>
<tr>
<td>Sutent (sunitinib)</td>
<td>Pfizer</td>
<td>PDGFR, VEGF, KIT, RET, FLT3, and CSF-1R inhibitor</td>
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<tr>
<td>Votrient (pazopanib)</td>
<td>Novartis (NYSE: NVS)</td>
<td>VEGF inhibitor</td>
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<td>Bayer (XETRA: BAYN.DE)</td>
<td>VEGF inhibitor</td>
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<td>Proleukin (aldesleukin)</td>
<td>Nestlé (VTX: NESN.VX)</td>
<td>High dose IL-2</td>
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<tr>
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<td>Novartis</td>
<td>mTOR inhibitor</td>
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<td>Opdivo (nivolumab)</td>
<td>Bristol-Myers Squibb (NYSE: BMY)</td>
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Source: LifeSci Capital

### Renal Cell Carcinoma – Market Information

The American Cancer Society estimates that 62,700 Americans will be diagnosed with kidney cancer in 2016 and more than 14,000 Americans will die from the disease. RCC makes up 90% of kidney cancer cases and accounts for approximately 56,500 diagnoses and 12,600 deaths annually. A physician at the University of Texas’s MD Anderson Cancer Center suggested that 25-33% of RCC patients have metastatic disease when they are first diagnosed, and 20-40% of individuals who start treatment for a localized tumor will become metastatic.

### Market Estimates for Archexin in RCC

Rexahn is developing Archexin as a second-line treatment in combination with Afinitor for RCC patients with metastatic disease. In 2015, sales of Afinitor were $1.6 billion globally and $900 million in the US across all indications including RCC. 2010 sales of Afinitor were $243 million after less than 2 years on the market and when the majority of sales were derived from RCC. Inlyta, another second-

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15 [https://www.urmc.rochester.edu/encyclopedia/content.aspx?ContentTypeID=35&ContentID=FAQKidneyCancer](https://www.urmc.rochester.edu/encyclopedia/content.aspx?ContentTypeID=35&ContentID=FAQKidneyCancer)
16 [http://www2.mdanderson.org/depts/oncolog/articles/12/5-may/5-12-compass.html](http://www2.mdanderson.org/depts/oncolog/articles/12/5-may/5-12-compass.html)
line RCC treatment, brought in $430 million in 2015 sales. Inlyta is only approved for RCC and has been on the market for less than 4 years. These sales numbers are an indication of the potential for Archexin in second-line RCC.

To get another estimate of the US sales potential for Archexin in second-line RCC, we have constructed the scenario analysis shown in Figure 9. Our main assumptions are outlined below:

- **Target population** – There are roughly 56,500 newly diagnosed RCC patients annually in the US. Approximately 29% of these patients are diagnosed with metastatic RCC, and 30% of patients with localized disease will eventually become metastatic and require a systemic therapy. Roughly 55% of patients relapse and may require a second-line therapy, translating into a target population of 15,600 patients annually.

- **Treatment duration** – We assume an average treatment duration of 7 months. This is based on the 7.4 month PFS seen in Cometriq’s Phase III METEOR study. We expect that the median PFS observed with Archexin would have to be competitive with Cometriq to penetrate the market. A 7 month PFS should also be sufficiently higher than single-agent Afinitor to demonstrate superiority.

- **Pricing** – We modeled sales using a price of $8,000 per month or $12,000 per month, which is a reasonable range considering the cost of new oncology drugs.

- **Penetration** – We use a peak penetration range of 20-40%. On the conservative side we have considered the number and quality of approved second-line therapies, the recent launches of Opdivo and Cometriq. On the aggressive side we acknowledge that despite the number of treatment options for RCC, none are curative. In fact, Rexahn has observed patients who failed both Opdivo and Cometriq in its Phase IIa clinical trial, suggesting that there may be an opportunity as a second- and third-line treatment depending on the patient.

Depending on the penetration and pricing, the peak opportunity in the US for Archexin in RCC could be $175 million to $524 million.

**Figure 9. Scenario Analysis of Market Potential of Archexin in RCC in the US**

<table>
<thead>
<tr>
<th>Eligible Patients (15,600 total)</th>
<th>20%</th>
<th>30%</th>
<th>40%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Price – Low ($8,000/month)</td>
<td>$56,000</td>
<td>$56,000</td>
<td>$56,000</td>
</tr>
<tr>
<td>Yearly Sales - Low</td>
<td>$175 M</td>
<td>$262 M</td>
<td>$349 M</td>
</tr>
<tr>
<td>Price High ($12,000/month)</td>
<td>$84,000</td>
<td>$84,000</td>
<td>$84,000</td>
</tr>
<tr>
<td>Yearly Sales - High</td>
<td>$262 M</td>
<td>$393 M</td>
<td>$524 M</td>
</tr>
</tbody>
</table>

*Source: LifeSci Capital*

Clinical Data Discussion for Archexin

Rexahn has completed clinical trials with Archexin as monotherapy and in combination with chemotherapy, and is currently enrolling a Phase IIa trial with metastatic RCC patients. The completed trials include a Phase I dose escalation study with Archexin monotherapy in patients with solid tumors, and a Phase IIa study combining Archexin with gemcitabine in metastatic pancreatic cancer patients. The ongoing study is a randomized Phase I/IIa trial testing Archexin in combination with Afinitor versus Afinitor monotherapy as a second-line treatment for patients with metastatic RCC.

The Phase I dose escalation study trial established the maximum tolerated dose of single-agent Archexin at 250 mg/m²/day. The pancreatic cancer trial was a single-arm, open-label, non-randomized study. The results showed a promising median overall survival of 9.1 months for patients treated with Archexin in combination with gemcitabine, which exceeds the historical OS for gemcitabine monotherapy of between 5.7 and 6.7 months. Rexahn’s current focus for Archexin is its ongoing Phase IIa trial in metastatic RCC. Results from the Phase I dose-escalation part of the study were presented at the American Association for Cancer Research (AACR) in April 2016 and there were initial signs of clinical activity as indicated by 3 of 10 patients experiencing tumor reduction. The randomized portion of the trial is currently enrolling patients.

Phase IIa Trial in Metastatic Pancreatic Cancer Patients

Study Design. This was a two-stage, open-label, non-randomized, single-arm Phase IIa study testing Archexin plus gemcitabine in metastatic pancreatic cancer. Stage 1 was a dose finding portion, and Stage 2 was a dose expansion phase using the maximum tolerated dose (MTD) identified from Stage 1. 31 patients were enrolled. They received 1,000 mg of gemcitabine once per week for 3 weeks followed by one week off, and the MTD of Archexin for 2 weeks followed by 1 week off. The primary endpoint of the study was overall survival. Secondary endpoints included tumor response, safety, and the Karnofsky performance scale, which classifies patients based on functional impairment.

Study Results. Data from this study were reported in 2012. Evaluable patients treated with Archexin plus gemcitabine had a median survival of 9.1 months. Caution should be applied when making cross trial comparisons due to inherent differences in patient characteristics, study conduct, and other factors. With that said, the historical median OS of metastatic pancreatic cancer patients treated with single-agent gemcitabine ranges from 5.7 to 6.7 months. This suggests that adding Archexin to gemcitabine may be beneficial over the single agent, and provides proof-of-concept for the continued development of Archexin. One caveat to note from the historical survival comparison is that patients enrolled in this study needed to have an estimated life expectancy of at least 6-months as assessed by the investigator. This may have led to a bias for healthier patients and contributed to the higher than historical median OS. In terms of safety, the most frequently reported adverse events were constipation, nausea, abdominal pain, and fever.

18 https://clinicaltrials.gov/ct2/show/NCT01028495
Phase I/IIa Trial in Metastatic Renal Cell Carcinoma

Rexahn is conducting an open-label, randomized Phase I/IIa study with Archexin in combination with Afinitor in patients with metastatic renal cell carcinoma who have failed a prior VEGF inhibitor. The Phase I portion identified the MTD of Archexin in combination with Afinitor as 250 mg/m²/day. Phase IIa is ongoing and patients are being randomized to Archexin plus Afinitor or Afinitor monotherapy. Full results are expected in the first half of 2017 and could be presented at AACR or ASCO 2017. Since the trial is open-label, initial data could be reported earlier.

Study Design. This is a Phase I/IIa study exploring Archexin in combination with Afinitor in patients with metastatic renal cell carcinoma who have failed a prior VEGF inhibitor.21 Phase I was a dose-escalation trial that evaluated three doses of Archexin in combination with Afinitor. Patients received 150, 200, or 250 mg/m²/day of Archexin as a continuous infusion for 14 days followed by 7 days off treatment. Up to 8, 3-week cycles were allowed. Afinitor was administered daily at 10 mg for 3 weeks per cycle. 3 patients received the first dose. After no toxicities were observed, 4 new patients were enrolled to receive the 200 mg/m²/day dose of Archexin. Finally, 3 patients received a dose of 250 mg/m²/day. Phase I was completed in January 2016, and the MTD was determined to be 250 mg/m²/day of Archexin plus the standard dose of Afinitor. Phase IIa is ongoing, and is an open-label, randomized, expansion study using the MTD from Phase I. 30 patients with metastatic RCC who have failed a prior VEGF treatment are expected to enroll and be randomized in a 2:1 ratio to receive:

- 250 mg/m²/day of Archexin for 2 weeks followed by 1 week off plus 10 mg/day of Afinitor.
- 10 mg/day of Afinitor.

The primary endpoint in Phase II is PFS. Secondary outcomes include safety, changes in clinical laboratory tests over time, and the change in tumor size.

Study Results. Results from part 1 of the study were presented at the American Association for Cancer Research (AACR) in April 2016.22 There were initial signals of clinical activity as evidenced by stable disease in 40% (4/10) of evaluable patients. The median duration of stable disease was 183.5 days. Three of these patients had reductions in tumor size that did not meet criteria for RECIST response, but we consider as demonstrations of the potential efficacy of Archexin. In fact, single lesion responses were observed. One of the patients dosed with 250 mg/m²/day of Archexin had a 32% tumor reduction and remains on treatment. Exploratory efficacy data from this study are shown in Figure 10. These initial data are interesting, especially considering that most patients were treated below the MTD. Ultimately, the ongoing randomized Phase IIa portion of the trial will provide a better idea of the clinical benefit of Archexin plus Afinitor versus Afinitor monotherapy in second-line metastatic RCC patients.

21 https://clinicaltrials.gov/ct2/show/NCT02089334
Pharmacokinetic data are shown in Figure 11. As shown in the left panel, there is a dose dependent rise in plasma levels of Archexin that peak and remain stable for a 25 hour period. This occurs roughly 5 hours following the start of treatment with both the 125 mg/m\(^2\)/day and 200 mg/m\(^2\)/day doses. The right panel depicts a dose dependent decrease of Archexin plasma levels following the cessation of treatment. Full clearance occurs roughly 25 hours after treatment is stopped.

In terms of safety, treatment with Archexin was generally safe and well tolerated for all three tested dose levels. 79% of adverse events were considered mild to moderate. There was 1 case of severe diarrhea, and another of severe...
platelet deficiency in the blood. Toxicities were mostly related to the combination treatment. No dose limiting toxicities occurred in the study.

**Competitive Landscape for RCC**

There are currently four treatments approved for second-line metastatic RCC. The leaders in this group in terms of sales are Novartis’s (NYSE: NVS) Afinitor (everolimus) and Pfizer’s (NYSE: PFE) Inlyta (axitinib). Bristol-Myers Squibb’s (NYSE: BMY) Opdivo (nivolumab) is expected to gain significant market share in second-line RCC following its demonstration of improved overall survival versus Afinitor and November 2015 approval by the FDA. Exelixis’ (NasdaqGS: EXEL) Cometriq (cabozantinib) was approved in May of 2016 based on data from its Phase III METEOR study showing a PFS of 7.4 months versus 3.8 months for Afinitor (p<0.0001). The objective response rate (ORR) for patients treated with Cometriq was 21% compared to 5% for Afinitor. One thing to note is that the safety profile of Cometriq raises concern, and may hamper physicians’ willingness to prescribe the agent. 60% (197/331) of patients receiving Cometriq required a dose reduction during the study compared to 25% (79/322) of patients treated with Afinitor. In addition, Grade 3 or 4 AEs occurred in 68% of patients treated with Cometriq, and 58% of patients treated with Afinitor.

In its Phase III pivotal trial, RCC patients treated with Opdivo had a median survival of 25.0 months compared to 19.6 months for patients treated with Afinitor (p=0.0018). The objective response rate for Opdivo in the study was 25% compared to 5% for Afinitor. In its first full year of approval, Opdivo sales from melanoma, non-small cell lung cancer, and RCC totaled $942 million. First quarter 2016 sales were $704 million. The excitement surrounding Opdivo is justified based on the clear demonstration of survival extension in the Phase III pivotal trial. Still, we note that most patients will ultimately relapse following Opdivo, and Rexahn has seen some patients enroll in its Phase IIA trial that failed Opdivo or Cometriq. There will continue to be a need for new therapies to address patients with resistance to approved drugs.

*Inlyta* is only approved as a second-line treatment for RCC. To give an indication of the potential for a new second-line RCC, *Inlyta* generated $430 million in global sales in 2015 after less than 4 years on the market. Each approved second-line RCC is shown in **Figure 12** along with its mechanism of action and approval year. Rexahn is currently studying Archexin in combination with Afinitor.

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**Figure 12. Approved Treatments for Second-Line RCC**

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>RCC Approval Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novartis</td>
<td>Afinitor (everolimus)</td>
<td>mTOR Inhibitor</td>
<td>2009</td>
</tr>
<tr>
<td>Pfizer</td>
<td>Inlyta (axitinib)</td>
<td>VEGF Inhibitor</td>
<td>2012</td>
</tr>
<tr>
<td>Bristol-Myers Squibb</td>
<td>Opdivo (nivolumab)</td>
<td>PD-1 Inhibitor</td>
<td>2015</td>
</tr>
<tr>
<td>Exelixis</td>
<td>Cometriq (cabozantinib)</td>
<td>MET, VEGFR, and RET inhibitor</td>
<td>2016</td>
</tr>
</tbody>
</table>

*Source: LifeSci Capital*

**RX-3117: Oral Next-Generation Nucleoside Analogue**

RX-3117 is an orally administered small molecule in development as a potential treatment for patients with pancreatic and bladder cancer. It is a next-generation nucleoside analogue that becomes activated in the body by uridine-cytidine kinase 2 (UCK2), an enzyme that plays a key role in RNA and DNA synthesis. UCK2 is overexpressed in several forms of cancer, but is minimally present in normal tissues. This cancer-specific expression could limit off-target activation of RX-3117 and therefore off-target side effects.\(^{25}\) It could also serve as a potential biomarker for upfront patient selection in future clinical trials. The chemical structure of RX-3117 is shown in Figure 13.

*Figure 13. RX-3117 Molecular Structure*

[Chemical structure image]

*Source: LifeSci Capital*

Rexahn has generated initial safety data with RX-3117 in a Phase I study, and preclinical studies suggest that it may be effective in several forms of cancer, including patients who are resistant to gemcitabine. The Company recently completed a Phase Ib study with RX-3117 in patients with advanced or metastatic solid tumors, and is currently conducting a Phase Ib/IIa study in pancreatic and bladder cancer patients. Full data from the Phase Ib will be announced later this year, and interim data from the Phase Ib/IIa study are expected in the second half of 2016.

**Mechanism of Action**

RX-3117 is a cytotoxic anti-metabolite that is designed to induce apoptosis by causing cellular arrest in the G₁ phase of the cell cycle. It is active in the body after being phosphorylated by UCK2, an enzyme that is overexpressed by several forms of cancer. The mechanism by which this occurs is shown in Figure 14. After administration, a nucleoside transporter called hENT mediates cellular uptake of RX-3117. Once inside of the cell, RX-3117 is phosphorylated. The diphosphate form (RX-DP) is reduced to dRX-DP by ribonucleotide reductase (RR), and dRX-DP can later be converted to a triphosphate form that can be incorporated into DNA. The triphosphate form can be incorporated into RNA and ultimately disrupt protein synthesis and DNA replication, triggering cell death.

![Figure 14. Proposed Mechanism of Action for RX-3117](source: Company Presentation)

Data presented at the 2016 American Association for Cancer Research also suggests that RX-3117 inhibits DNA methyltransferase 1 (DNMT1), which is the same target as the approved drugs for myelodysplastic syndromes, *Vidaza* (azacitidine) and *Dacogen* (decitabine). DNMT1 inhibition may contribute to the cytotoxic nature of RX-3117 and could potentially serve as a biomarker in future clinical trials.

**Potential Use of RX-3117 in Gemcitabine Resistant Cancers.** Gemcitabine is a cytotoxic anti-metabolite that is commonly used to treat patients with several cancers including pancreatic, non-small cell lung, bladder, soft-tissue, metastatic breast, and ovarian. When combined with Celgene’s (NasdaqGS: CELG) *Abraxane* (paclitaxel protein-bound particles for injectable suspension), it is considered the standard of care for pancreatic cancer, and is often used in combination with cisplatin for bladder cancer. Attempts to create an oral formulation of the drug have been unsuccessful, and so only an intravenous version is available.

Many patients receiving gemcitabine eventually become resistant to treatment. Rexahn estimates that this may occur in between 25% and 40% of individuals. Some of the key causes for resistance include alterations in the human equilibrative nucleoside transporter-1 (hENT1) and genes responsible for gemcitabine metabolism like deoxycytidine kinase (dCK) and ribonucleoside reductase M1 and M2.27,28 RX-3117 may be able to overcome some of these resistance mechanisms. In fact, RX-3117 is activated by uridine cytidine kinase 2 (UCK2) instead of dCK, meaning that patients with gemcitabine resistance due to mutations in dCK may still be sensitive to RX-3117.

In preclinical studies, RX-3117 has shown promising activity in gemcitabine resistant cancer cells. If these results can be replicated in human studies, RX-3117 may provide a favorable alternative for patients who are gemcitabine resistant. We do acknowledge that RX-3117 is also transported through hENT1, and may not be active in gemcitabine resistant cancers due to hENT1 mutations. Despite this, tumor regression has been observed in several gemcitabine resistant xenograft models, suggesting that alternative transport mechanisms may be working to deliver RX-3117 into the cell.

A competing approach being studied to combat gemcitabine resistance is the combination of GlaxoSmithKline’s (NYSE: GSK) *Retrovir* (zidovudine) and gemcitabine. *Retrovir* is a nucleoside reverse transcriptase inhibitor (NRTI) that is approved to treat HIV, and a recent study in mice suggests that it may resensitize gemcitabine-resistant pancreatic cancer cells.29 Both epithelial-to-mesenchymal transition (EMT)-like phenotype and down regulation of hENT1 are common causes for gemcitabine resistance. An important signaling event for resistance is the activation of the AKT-GSK3β-Snail pathway, and treatment with zidovudine may inhibit this pathway. Despite the encouraging preclinical results, we have not identified any human studies that have commenced with this combination.

**Previous Partnership with Teva.** Between September 2009 and August 2013 Rexahn had a research and exclusive license option agreement with Teva Pharmaceutical (NYSE: TEVA) for RX-3117. Teva decided to not exercise its licensing option for RX-3117 due to strategic reasons, and Rexahn as a result retained full global development and commercialization rights. Notably, Teva shifted the focus of its pipeline away from oncology around this timeframe.

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and abandoned the development of multiple cancer agents. Teva also sold several solid tumor candidates to Ignyta, Inc. (NasdaqCM: RXDX) in March 2015, further indicating that the company is divesting its oncology pipeline. Teva funded the preclinical development of RX-3117 and filed an IND for the drug, and Rexahn is now pursuing clinical development.

**Preclinical Studies with RX-3117**

Below we discuss preclinical experiments with RX-3117 that lay the groundwork for a potential biomarker enrichment strategy using UCK2 expression levels. They also provide evidence for RX-3117’s activity in gemcitabine-resistant patients.

**RX-3117 Activity Correlated with UCK Expression.** The relationship between RX-3117’s efficacy and UCK levels was evaluated in three xenograft models using the following cell lines: Colo 205 human colorectal cancer, H460 human non-small cell lung cancer, and BxPC3 human pancreatic cancer. Mice were treated with 500 mg/kg of RX-3117 three times per week for 3 cycles. UCK activity was measured in each tumor model and was compared to the degree of tumor growth inhibition. As shown in Figure 15, the BxPC3 tumor model had low levels of UCK activity, and RX-3117 was unable to inhibit tumor growth. Notably, BxPC3 has low dCK activity, and as a result, is also resistant to treatment with gemcitabine. In contrast, both the H460 and Colo205 tumor models had higher levels of UCK expression relative to BxPC3, and had tumor growth inhibition of 78% and 100%, respectively, compared to a control. The strong association between UCK levels and the efficacy of RX-3117 may allow Rexahn to employ a biomarker strategy in the future to identify patients who will benefit most from treatment.

**Figure 15. Correlation Between RX-3117 Efficacy and UCK Activity**

![Figure 15](https://example.com/f15.png)

Source: Yang, M.Y. et al., 2014

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30 Yang, M.Y. et al., 2014. A novel cytidine analog, RX-3117, shows potent efficacy in xenograft models, even in tumors that are resistant to gemcitabine. *Anticancer Research, 34*(12), pp6951-6959.

**Strong Activity Observed in Primary Human Pancreatic Cancer Model.** RX-3117 was tested in a primary human pancreatic cancer line called CTG-0298. This line was chosen based on its high UCK activity and resistance to gemcitabine. Fragments of the human tumor, which were initially grown in carrier mice, were implanted into nude mice. Nude mice lack functional immune systems and can tolerate cells from other species. When tumor volume reached between 80 and 130 mm³, the mice were sorted into 1 of 4 groups and administered the following agents:

- Vehicle 3 times a week for 3 weeks.
- 80 mg/kg of gemcitabine once every 3 days for 4 weeks.
- 150 mg/kg of RX-3117 3 times a week for 3 weeks.
- 300 mg/kg of RX-3117 3 times a week for 3 weeks.

As shown in **Figure 16**, there was a dose dependent reduction in tumor volume with increasing concentrations of RX-3117. The degree of tumor reduction was greater with RX-3117 than vehicle or gemcitabine.

![Figure 16. RX-3117 Activity in a Primary Human Pancreatic Cancer Model](source)

*Source: Yang, M.Y. et al., 2014*

**Activity Observed in Gemcitabine Resistant Cancers.** RX-3117's anti-tumor activity was evaluated in human xenograft models that are insensitive to gemcitabine.³² Colo205 colorectal cancer, H460 non-small cell lung carcinoma (NSCLC), H69 small cell lung carcinoma (SCLC), and CaSki cervical cancer cells were introduced subcutaneously into athymic nude mice. When the tumors reached a size of 80-130 mm³, mice were treated according to the dose schedules described in **Figure 17**. Gemcitabine was delivered via intraperitoneal injection and RX-3117 was oral.

Figure 17. Dosing Regimen for Gemcitabine Insensitive Cell Lines

<table>
<thead>
<tr>
<th>Cancer Cell Line</th>
<th>Gemcitabine Dose</th>
<th>RX-3117 Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colo205 (colorectal)</td>
<td>120 mg/kg every 3rd day x4</td>
<td>500 mg/kg 3 times/week x3</td>
</tr>
<tr>
<td>H460 (NSCLC)</td>
<td>120 mg/kg every 3rd day x4</td>
<td>300 mg/kg 3 times/week x3 or 500 mg/kg 3 times/week x3</td>
</tr>
<tr>
<td>H69 (SCLC)</td>
<td>80 mg/kg every 3rd day x10</td>
<td>300 mg/kg 3 times/week x3</td>
</tr>
<tr>
<td>CaSki (cervical)</td>
<td>80 mg/kg intraperitonealy every 3rd day x10</td>
<td>150 mg/kg orally 3 times/week x3</td>
</tr>
</tbody>
</table>

*Source: LifeSci Capital*

Results are shown in Figure 18. Treatment with RX-3117 in gemcitabine insensitive cancer led to greater inhibition of tumor growth compared to gemcitabine. The CaSki cancer cells were highly resistant to treatment with gemcitabine, showing no tumor growth inhibition, whereas treatment with RX-3117 inhibited tumor growth by 74%. This data supports the notion that RX-3117 may be effective in gemcitabine resistant cancers.

Figure 18. RX-3117 Tumor Growth Inhibition in Gemcitabine Insensitive Cancers

*Source: Yang, M.Y. et al., 2014*
Safety Profile. Rexahn presented preliminary Phase Ib safety data for RX-3117 in September of 2015. Treatment was overall safe and well tolerated. The most frequently reported adverse events included mild to moderate fatigue, nausea, and diarrhea, and anemia.

Target Indications for RX-3117

Rexahn is developing RX-3117 as a treatment for patients with pancreatic cancer and bladder cancer. Promising preclinical activity with RX-3117 in pancreatic and bladder cancer cell lines provides the rationale for the Company to initially focus on these indications. Both pancreatic and bladder cancer also have high rates of gemcitabine resistance, and RX-3117 has demonstrated tumor growth inhibition in gemcitabine resistant cancer cells. There is also a significant need for new treatments for pancreatic and bladder cancer patients, as nearly 60,000 patients are expected to die from the diseases in the US in 2016.

Pancreatic Cancer

Pancreatic cancer is one of the most deadly forms of cancer, leading to approximately 42,000 deaths per year in the US.\(^3\) It is the fourth most common cause of cancer-related deaths in the US, and has a 5-year survival rate of only 7%. The poor prognosis is a result of several factors, including the fact that most of the estimated 53,000 new patients per year in the US are diagnosed at a late stage due to the lack of early symptoms and no reliable screening tests. Symptoms include severe abdominal pain, jaundice, loss of appetite, weight loss, diarrhea, and nausea. Diagnosis of pancreatic cancer is generally made during evaluation of symptoms, and may include analysis of serum CA19-9 levels. CA19-9 is often elevated in those with pancreatic cancer, but the biomarker is rarely detected in asymptomatic people.

The molecular pathogenesis of pancreatic adenocarcinoma has been well characterized. Almost all tumors carry an initiating mutation in the KRAS oncogene, while mutations in TP53, SMAD4 and CDKN2A are predominant. c-Kit has recently been proposed to enhance invasiveness of pancreatic cancer.\(^3\)\(^4\) Despite a strong understanding of the underlying genetics, there has not been a corresponding advance in targeted therapeutics and the associated gains in patient outcomes.

Treatment includes surgery, radiation, and chemotherapy, but only 20% of patients are eligible for surgery. This is due to the fact that by the time of diagnosis, most tumors have spread beyond the pancreas, and metastatic disease is substantially more difficult to treat than localized tumors. Approved therapeutics along with their target are shown in Figure 19. Celgene’s (NasdaqGS: CELG) Abraxane (paclitaxel) was approved for pancreatic cancer in 2013 based on results from its Phase III study showing a median overall survival of 8.5 months when combined with gemcitabine compared to 6.7 months for gemcitabine alone.\(^3\)\(^5\) Notably, all approved agents are chemotherapies with the exception of Astellas’ (TYO: 4503) Tarceva (erlotinib), which targets the epidermal growth factor receptor (EGFR).

\(^3\) http://www.cancer.org/cancer/pancreaticcancer/detailedguide/pancreatic-cancer-key-statistics


Bladder Cancer

Bladder cancer is characterized by tumors forming inside the lining of the bladder and sometimes spreading to other tissues. According to the American Cancer Society, it is the fifth most common type of cancer in the US with an estimated 77,000 new cases and 16,000 deaths expected in 2016.36 Men are three times more likely to develop the disease than women, and elderly white men are most commonly afflicted. The prognosis and recommended treatment depend on the stage of the cancer, and many patients experience recurrence after initial treatment, leading to a need for ongoing follow-up and surveillance. Treatments include bladder tumor resection, chemotherapy, radiation, immunotherapy, and complete bladder removal.37 There have been no major treatment advances for patients with bladder cancer in nearly 30 years. As one of the most expensive cancers to treat per patient from diagnosis until death,38 it is burdensome on the healthcare system.

According to the National Cancer Institute, the overall 5-year survival rate for bladder cancer patients is 77%. This is because most bladder cancers are found during the non-invasive stage and can be treated successfully. If the cancer has become invasive or metastatic, the survival rate drops dramatically, as seen in Figure 20.

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36 http://www.cancer.org/cancer/bladdercancer/detailedguide/bladder-cancer-key-statistics
Market for Pancreatic and Bladder Cancer

Pancreatic Cancer Market. More than 53,000 people are expected to be diagnosed with pancreatic cancer in the US alone this year, resulting in an estimated 42,000 deaths. Gemcitabine has been used for nearly two decades as a first-line treatment of advanced or metastatic pancreatic cancer. Celgene’s (NasdaqGS: CELG) Abraxane (protein bound paclitaxel) in combination with gemcitabine recently gained FDA approval for pancreatic cancer and has become the standard of care based on an enhanced survival benefit relative to other gemcitabine combination treatments. Roche/Genentech’s (VRTX.ROG.VX) Tarceva (erlotinib) is approved as a first-line treatment in combination with gemcitabine, although modest improvements to survival have led to minimal use in pancreatic cancer. The sales of drugs on the market for pancreatic cancer are displayed in the Figure 21. Note that sales for Tarceva and Abraxane are primarily driven by other indications.

Figure 21. Drugs on Market for Metastatic Pancreatic Cancer

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Approval Year for Pancreatic Cancer</th>
<th>2015 Sales (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemzar (gemcitabine)</td>
<td>Eli Lilly/generic</td>
<td>1996</td>
<td>-</td>
</tr>
<tr>
<td>Tarceva (erlotinib)</td>
<td>Roche</td>
<td>2007</td>
<td>$1,182*</td>
</tr>
<tr>
<td>Abraxane (paclitaxel)</td>
<td>Celgene</td>
<td>2013</td>
<td>$968*</td>
</tr>
<tr>
<td>Onivyde (irinotecan)</td>
<td>Merrimack</td>
<td>2015</td>
<td>$4</td>
</tr>
</tbody>
</table>

*includes sales for all indications

Source: Company Reports
The global pancreatic cancer market is expected to exceed $1 billion by the end of the decade. In order to gain market share, new treatments will need to show significant improvements in overall survival or have a superior toxicity profile compared to currently approved treatments. The toxicity component is important considering that Abraxane has a boxed warning for bone marrow suppression and is associated with other severe adverse events.

**Bladder Cancer Market.** According to the American Cancer Society, bladder cancer is the fifth most common cancer in the US with approximately 77,000 new cases expected to be diagnosed in 2016. A key issue for bladder cancer is the high rate of recurrence, for which limited treatment options are available beyond complete bladder removal.

The current market in the US and Europe for bladder cancer drug sales is approximately $250 million and is expected to grow to about $650 million by 2017, with the US generating over 50% of the sales. The market is relatively small for a disease with such a high incidence rate due to the fact that most bladder cancer drugs are generic. There has not been a new approved bladder cancer drug in over 25 years. However, the value of the overall treatment market is likely to expand in the near future, driven by the emergence of new branded chemotherapies and immunotherapy agents such as Roche’s (VTX: ROG.VX) atezolizumab. Roche completed a successful Phase III clinical trial with atezolizumab in metastatic bladder cancer and has filed an NDA.

**Clinical Data Discussion for RX-3117**

Rexahn has completed a Phase I trial with RX-3117 in advanced cancer patients and a Phase Ib study in patients with advanced or metastatic solid tumors. A Phase Ib/IIa study in pancreatic and bladder cancer patients is currently ongoing. Interim results from the completed Phase Ib trial were presented at the European Cancer Congress (ECC) in September 2015 showing signs of anti-tumor activity with single-agent RX-3117. A recommended Phase II dose was identified and Rexahn initiated a Phase Ib/IIa study in March 2016. Interim data from this study are expected in the second half of 2016.

**Completed Phase Ib Trial in Advanced Solid Tumors**

Interim results of this open-label Phase Ib study were presented at the 2015 ECC conference. RX-3117 was generally well tolerated in patients with several types of advanced cancer, and a recommended Phase II dose and dosing schedule were identified. Initial signals of clinical activity were also observed, as 5 of 27 patients had stable disease for 100 days or more. Full Phase Ib data are expected to be presented at a medical meeting in 2016.

**Phase Ib Trial Design.** This is an open-label, single arm, dose-finding Phase Ib study evaluating single agent RX-3117 in patients with advanced or metastatic solid tumors. Unlike a standard 3+3 dose-escalation design, this trial enrolled a single patient at initial doses until the appearance of a related Grade 2 or higher adverse event (AEs). After a Grade 2 AE occurred, 3 patients were treated at future doses. Doses ranged from 30 to 2,000 mg.

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39 http://www.cancer.org/cancer/bladdercancer/detailedguide/bladder-cancer-key-statistics
40 https://clinicaltrials.gov/ct2/show/NCT02030067
30 patients were expected to enroll in the study and be treated with up to eight 4-week treatment cycles of RX-3117. Each cycle consists of RX-3117 dosed 3 times per week for 3 weeks followed by 1 week off. A protocol adjustment was made during the study where patients received RX-3117 five or seven times per week. This was done to increase total drug exposure. The primary endpoint is safety. Secondary endpoints include pharmacokinetics and change in tumor size at weeks 8, 16, and 32.

**Phase Ib Interim Results.** Interim results were presented at the ECC in September 2015.\(^{41}\) There were no dose limiting toxicities reported at doses of up to 2,000 mg 3 times per week, which was the maximum dose level tested. The most frequent adverse events (AEs) were fatigue 52% (13/25), nausea 24% (6/25), diarrhea 20% (5/25), and anemia 12% (3/25), and they were mild to moderate.

In terms of pharmacokinetics, RX-3117 was absorbed rapidly and reached peak plasma concentrations after 2 to 3 hours. The half-life was not dose dependent and the mean half-life was between 11.6 to 16.2 hours for the 60 to 1,500 mg doses. The C\(_{\text{max}}\) and total plasma exposure increased in a largely linear fashion during dose escalation, and PK modeling suggested that a more frequent dosing schedule of 5 times per week would ensure more sustained RX-3117 levels compared to 3 times per week. The favorable safety profile at doses of up to 2,000 mg 3 times per week also indicated that it was worth exploring additional dosing regimens to boost drug exposure. As is discussed below, Rexahn has chosen 700 mg 5 times per week as the dose for the ongoing Phase Ib/IIa trial.

Even with the suboptimal dosing schedule, there were initial signals of clinical activity. Five of 27 patients experienced stable disease. All of these subjects were on treatment for more than 100 days, and one breast cancer patient was on therapy for 276 days.

**Phase Ib/IIa Trial Design.** This is an open-label, single-arm, Phase Ib/IIa study in patients with relapsed or refractory pancreatic cancer and advanced bladder cancer. This is a two-part study. In the first part, 10 patients with each type of cancer will be enrolled and receive 700 mg of oral RX-3117 5 times per week on a 3 weeks on, 1 week off dosing schedule. This will occur for 4 cycles or until disease progression. If responses are observed within the first 10 evaluable patients, 40 addition patients will be enrolled in the second part of the trial. The primary endpoints of the study are progression free survival (PFS), objective clinical response rate, and reduction in tumor size. Interim results are expected in the second half of 2016. The true timing of initial data depends on the results from patients in part 1 of the study. For example, based on the two stage design, if the first few patients experience tumor responses or extended progression free survival, Rexahn could trigger the enrollment of additional patients in part 2 and disclose the activity from part 1. Otherwise, we expect that the European Society for Medical Oncology (ESMO) 2016 is a possible venue for initial Phase Ib/IIa data.

**Supinoxin (RX-5902): Phosphorylated p68 Inhibitor**

Supinoxin is a highly potent, orally available inhibitor of phosphorylated p68 (phospho-p68) and is in development for patients with cancer. Phospho-p68 is a unique target and appears to be exclusively expressed in cancer cells. We are unaware of any clinical programs targeting phospho-p68 other than Supinoxin. Preclinical experiments suggest that Supinoxin has activity in more than 100 human cancer cell lines, including difficult-to-treat cancers and tissue

types representing large market indications. Rexahn is currently conducting a Phase I trial and presented interim clinical data at the 2015 European Cancer Congress showing a favorable safety profile and indications of preliminary clinical activity. The Company is planning to launch a Phase Ib/IIa trial in the third quarter of 2016 that will enroll patients with triple negative breast cancer and relapsed advanced ovarian cancer.

Supinoxin was first identified from a screen of 1,200 quinoxalinyl-piperazine compounds for anti-cancer activity. A chemical structure of the product candidate is shown in Figure 22. It had cytotoxic effects against a paclitaxel-resistant colorectal carcinoma cell line and synergistic activity in combination with known cancer drugs such as doxorubicin, cisplatin, and gemcitabine. The IC_{50} for several human cancer cells lines was between 11 and 21 nM. Supinoxin also had superior bioavailability relative to other quinoxalinyl-piperazine candidates that have anti-cancer activity. In data collected from Sprague-Dawley male rats, Supinoxin showed 83% oral bioavailability and had a half-life of 7.9 hours.

**Figure 22. Chemical Structure of Supinoxin**

![Supinoxin Structure](image)

*Source: LifeSci Capital*

**Mechanism of Action**

Supinoxin’s activity is mediated through binding to phosphorylated p68, which is an RNA helicase that is overexpressed in rapidly dividing cells including colorectal adenocarcinomas. The association between p68 and cancer is thought to be specific to the phosphorylated versions, and phospho-p68 expression is generally not found in normal cells. Phosphorylation of one specific site, tyrosine 593 (Y593), can trigger signaling through the Wnt/β-...

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β-catenin pathway and induce epithelial to mesenchymal transition. The signaling occurs independently of the presence of the ligand Wnt, which typically triggers the pathway as shown in Figure 23. When Wnt is not bound to the frizzled receptor and LRP 5/6, a protein complex leads to phosphorylation of β-catenin and its degradation via the proteasome. In the presence of Wnt, the destruction complex becomes tethered to the plasma membrane. Disheveled (DSH) blocks the phosphorylation of β-catenin by glycogen synthase kinase 3 (GSK), and β-catenin enters the nucleus where it binds to the co-transcription factor TCF and induces genes that control several processes such as cell proliferation and migration.

Figure 23. Signaling of Wnt/β-catenin Pathway via PDGF and Phosphorylated p68

Phospho-p68 is involved in non-canonical β-catenin signaling. Signaling through platelet derived growth factor (PDGF) activates the c-Abl protein, which leads to phosphorylation of p68. Phospho-p68 displaces Axin from the destruction complex and inhibits phosphorylation of β-catenin by GSK. It ultimately leads to the expression of β-

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catenin-induced target genes without the need for Wnt. Some genes induced by phospho-p68 include cyclin D1 and c-Myc, which are critical for cell proliferation.\textsuperscript{49} Recent in vitro experiments found that treatment of cells with Supinoxin leads to downregulation of β-catenin-induced target genes, validating the pathway as a key mediator of Supinoxin activity.\textsuperscript{50}

Supinoxin Preclinical Studies

Supinoxin is supported by promising preclinical data validating its cytotoxic effect on cancer cells. In December 2015, results from a mouse model of triple negative breast cancer (TNBC) were presented at the San Antonio Breast Cancer Symposium.\textsuperscript{51} The data, which are discussed in more detail below, show that Supinoxin inhibits tumor growth and can prolong survival in a xenograft model of TNBC. They also provide supporting data that Supinoxin exerts its activity through phospho-p68 binding. Additional preclinical data were presented at scientific conferences in January 2016.\textsuperscript{52,53} They indicate that Supinoxin is active in pancreatic cancer and renal cell carcinoma cell lines and xenograft models.

Tumor Growth Inhibition and Impact on Survival. Immunodeficient mice were injected subcutaneously with MDA-MB-231, a human triple negative breast cancer cell line. The cancer cells were allowed to expand to an average size of 100 mm\(^3\) and then the mice were treated with a vehicle control solution, Abraxane, or 1 of 3 doses of Supinoxin. Seven mice were treated per group. Abraxane is approved for metastatic breast cancer and mice received intravenous administration at 5 mg/kg twice weekly for 3 weeks. Supinoxin was dosed orally at 160, 320, or 600 mg/kg once per week for 3 weeks. As shown in Figure 24, there was a dose-dependent impact on tumor growth inhibition. Furthermore, treatment with 320 and 600 mg/kg of Supinoxin led to a significant delay in the percentage of tumor growth compared to vehicle treated mice. (p≤0.01 and p≤0.001, respectively). For mice in the 600 mg/kg dose group, the percentage of tumor growth inhibition relative to control was 83% (p≤0.01). There was not a significant difference in tumor growth delay or inhibition between the Abraxane and vehicle control groups.

\textsuperscript{49} Yang, L. et al., 2007. Phosphorylation of p68 RNA helicase plays a role in platelet-derived growth factor-induced cell proliferation by up-regulating cyclin D1 and c-Myc expression. The Journal of Biological Chemistry, 282(23), pp16811-16819.


\textsuperscript{51} Yang, M.Y. et al., 2015. The anticancer effects of Supinoxin (RX-5902) in triple-negative breast cancer MDA-MB-231 through phosphorylated p68 on Tyr593. 38th Annual San Antonio Breast Cancer Symposium.

\textsuperscript{52} Bok Lee, Y. et al., 2016. The anticancer effects of Supinoxin (TX-5902) in renal cell carcinoma. ASCO Genitourinary Cancers Symposium.

\textsuperscript{53} Bok Lee, Y. et al., 2016. The anticancer effects of Supinoxin (TX-5902) in pancreatic carcinoma. ASCO Gastrointestinal Cancers Symposium, Abstract #238.
Supinoxin treatment also led to an increase in survival relative to vehicle- and *Abraxane*-treated mice. The data are shown in Figure 25. All mice survived at least 15 days post-treatment. By 35 days post-treatment, no mice treated with vehicle were alive. In contrast, at 35 days post-treatment more than 80% of mice treated with the highest dose of Supinoxin were alive.

**Figure 25. Survival Following Supinoxin Treatment in Mouse Model of Triple Negative Breast Cancer**

*Source: Yang, M.Y. et al., 2015*
Evidence of phospho-p68 as Supinoxin Target. Supinoxin has anti-cancer activity in over 100 cell lines, and as discussed above, can inhibit tumor growth and prolong survival in mouse models of triple negative breast cancer. It is thought to work via binding to phosphorylated p68, which blocks downstream signaling pathways that lead to cell proliferation and migration. A gene knockdown experiment was performed in a TNBC mouse model to confirm that Supinoxin works through p68. A small interfering RNA (siRNA) was used to reduce p68 expression in the TNBC cell line MDA-MB-231. Mice were injected with 1 of 3 cells: untreated MDA-MB-231 (Un-tfx), MDA-MB-231 containing a control siRNA with no activity against p68 (si-NS), and MDA-MB-231 containing the p68 siRNA and thus with low levels of p68 (si-p68). All mice were then treated with Supinoxin and the level of tumor reduction was measured, as shown in Figure 26.

Figure 26. Impact of p68 Downregulation on Activity of Supinoxin

![Figure 26](image)

Source: Yang, M.Y. et al., 2015

As expected, the Un-tfx group showed a robust inhibition of growth relative to mice not treated with Supinoxin. The si-NS group also showed greater than 60% tumor growth inhibition. However, the si-p68 group that was treated with Supinoxin and had reduced levels of p68 had less robust tumor growth inhibition. In other words, reduction of p68 eliminated the effect of Supinoxin, which confirms that Supinoxin is acting through this protein.

Target Indications for Supinoxin

Triple Negative Breast Cancer

Breast cancer is the second most common cancer in women, and an estimated 246,660 women will be diagnosed with an invasive form of the disease in 2016. Triple-negative breast cancer (TNBC) is an aggressive form of invasive breast cancer that makes up between 10% and 20% of all cases.54 This translates into an estimated 25,000 to 50,000 new cases of TNBC annually. Unlike most forms of breast cancer, TNBC cells do not express the estrogen,

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progesterone, or HER-2/neu receptors. As a result, hormonal therapies and HER-2 targeted treatments such as Roche's Herceptin (trastuzumab) are ineffective against the disease. Systemic treatments for TNBC are currently limited to cytotoxic chemotherapy and radiation therapy, which are often followed by lumpectomy or mastectomy. Compared to other forms of breast cancer, TNBC is more likely to spread to other areas of the body, and there is a higher probability of recurrence following treatment. The 5-year survival for the TNBC is 77% compared to 93% for women with other forms of breast cancer.

Due to the lack of treatments and high incidence of TNBC, there are several treatments in Phase III development. They are shown in Figure 27. Agents that target PD-1, PD-L1, and poly ADP ribose polymerase (PARP) have had success treating other forms of cancer, and have garnered the most attention of the group. AstraZeneca’s (NYSE: AZN) PARP inhibitor Lynparza (olaparib) is currently approved in ovarian cancer for patients that have a BRCA mutation, which occurs in roughly 11% of TNBC patients. On the other hand, PD-1 inhibitors have been successful in treating solid tumors like non-small cell lung cancer and renal cell carcinoma. Merck’s (NYSE: MRK) Keytruda (pembrolizumab) is being evaluated as a single agent treatment for TNBC, whereas Roche’s (VTX: ROG.VX) atezolizumab is being tested in combination with Abraxane. Despite the presence of these promising agents in development, we believe that each will only capture a portion of the full TNBC market, allowing several treatments to be supported at once in the space. Supinoxin has the potential to become a targeted treatment for TNBC based on its activity against p68 phosphorylation.

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56 Bauer, K.R. et al., 2007. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype. Cancer, 109(9), pp1721-1728.
### Figure 27. Programs in Phase III Development for TNBC

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roche (VTX: ROG.VX)</td>
<td>Atezolizumab</td>
<td>PD-L1&lt;sup&gt;58&lt;/sup&gt;</td>
</tr>
<tr>
<td>SynCore Biotech (private)</td>
<td>EndoTAG-1</td>
<td>Tubulin*</td>
</tr>
<tr>
<td>Nektar Therapeutics (NasdaqGS: NKTR)</td>
<td>Etitinotecan pegol</td>
<td>Topoisomerase I&lt;sup&gt;59&lt;/sup&gt;</td>
</tr>
<tr>
<td>Merck (NYSE: MRK)</td>
<td>Keytruda</td>
<td>PD-I&lt;sup&gt;60&lt;/sup&gt;</td>
</tr>
<tr>
<td>AstraZeneca (NYSE: AZN)</td>
<td>Lynparza (olaparib)</td>
<td>PARP&lt;sup&gt;61&lt;/sup&gt;</td>
</tr>
<tr>
<td>Amgen (NasdaqGS: AMGN)</td>
<td>Nexavar (sorafenib)</td>
<td>VEGF&lt;sup&gt;62&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tesaro (NasdaqGS: TSRO)</td>
<td>Niraparib</td>
<td>PARP&lt;sup&gt;63&lt;/sup&gt;</td>
</tr>
<tr>
<td>Medivation (NasdaqGS: MDVN)</td>
<td>Talazoparib</td>
<td>PARP&lt;sup&gt;64&lt;/sup&gt;</td>
</tr>
<tr>
<td>Abbvie (NYSE: ABBV)</td>
<td>Veliparib</td>
<td>PARP&lt;sup&gt;65&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

*Phase III trial expected to begin soon

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**Source: LifeSci Capital**

### Ovarian Cancer

The National Cancer Institute estimated that there would be about 14,000 deaths due to ovarian cancer in the US in 2015 along with 21,300 new cases, although studies suggest that the rate of incidence is slowly declining.<sup>66</sup> Ovarian cancer can be broken down into four stages. If ovarian cancer is only in one or both of the ovaries, it is characterized as Stage I. Stage II is when the cancer spreads to other parts of the pelvic area, including the fallopian tubes, uterus, bladder, colon, or rectum. When the cancer is detected early in Stage I or Stage II, the 5-year survival rate is 95% and 65%, respectively. In general, treatment for ovarian cancer involves surgery with chemotherapy or radiotherapy, although only 40% of women are cured using existing treatments, and most of these patients have early-stage disease. If the cancer has spread beyond the ovaries to the abdomen or lymph nodes in the back of the abdomen, it is Stage III. Stage IV is the most advanced stage of ovarian cancer, when cancer has reached distant organs or lymph nodes.

Nearly all women diagnosed with ovarian cancer undergo surgery by an obstetrician/gynecologist, general surgeon, or gynecologic oncologist. Surgeries usually involve removing the ovaries, fallopian tubes, and uterus. Patients receive intravenous or intraperitoneal chemotherapy following surgery, except for those with Stage IA and IB disease, who are instead monitored. The most common agents are combinations of paclitaxel, docetaxel, and platinum-based chemotherapies such as cisplatin and carboplatin. Systemic therapies used for the treatment of ovarian cancer are listed in Figure 28. Dose levels and schedules are adjusted based on patient characteristics such as:

58 https://clinicaltrials.gov/show/NCT02425891  
59 https://clinicaltrials.gov/show/NCT01492101  
60 https://clinicaltrials.gov/show/NCT02555657  
61 https://clinicaltrials.gov/show/NCT02032823  
62 https://clinicaltrials.gov/show/NCT01234337  
63 https://clinicaltrials.gov/show/NCT01905592  
64 https://clinicaltrials.gov/show/NCT01945775  
65 https://clinicaltrials.gov/show/NCT02032277  
as disease Stage, location of tumor, age, and performance status. New combinations of chemotherapy are often given following initial treatment failure such that patients may receive 3 or more lines of chemotherapy. Avastin (bevacizumab) is the only agent FDA-approved for patients with platinum-resistant recurrent ovarian cancer in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan. In pivotal trials the combination therapy significantly improved progression free survival (PFS) compared to chemotherapy alone.

**Figure 28. Systemic Therapies for Ovarian Cancer**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>Generic</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Generic</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Liposomal doxorubicin</td>
<td>Generic</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Topotecan</td>
<td>Generic</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Generic</td>
<td>Platinum-based chemotherapy</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>Generic</td>
<td>Platinum-based chemotherapy</td>
</tr>
<tr>
<td><strong>Avastin</strong> (bevacizumab)</td>
<td>Roche/Genentech (VTX: ROG.VX)</td>
<td>VEGF inhibitor</td>
</tr>
<tr>
<td><strong>Lynparza</strong> (olaparib)</td>
<td>AstraZeneca (NYSE: AZN)</td>
<td>PARP inhibitor</td>
</tr>
</tbody>
</table>

*Source: LifeSci Capital*

In December 2014 the FDA granted accelerated approval to AstraZeneca’s Lynparza (olaparib), a PARP inhibitor. It is indicated for patients with advanced ovarian cancer that have failed 3 or more lines of chemotherapy and who have BRCA mutations. Approval was based on a trial with 137 patients where single-agent Lynparza led to an overall response rate of 34%. Survival data will be collected in Phase III trials to support a full approval. Based on the response rate from the trial, 66% of patients who have failed 3 or more lines of chemotherapy also fail Lynparza, which highlights the serious unmet need for new therapies to treat late-state recurrent ovarian cancer patients.

**Market Estimate for TNBC and Advanced Ovarian Cancer**

**Triple Negative Breast Cancer Market.** TNBC is an aggressive form of invasive breast cancer. An estimated 25,000 to 50,000 new cases occur annually in the US. Approximately 37% of cases are locally advanced or metastatic and patients would benefit from systemic therapies beyond surgery. Systemic treatments for TNBC are currently limited to cytotoxic chemotherapy and radiation therapy. The lack of innovative, targeted treatments for TNBC patients such as Herceptin has led to poorer outcomes compared to other types of invasive breast cancer. Based on one study of 1,601 women with breast cancer, patients with TNBC have a significantly higher risk of distant recurrence (p<0.0001) and death (p<0.001) within 5 years of diagnosis compared to patients with other types of breast cancer.67 Another study of women who received neoadjuvant chemotherapy led to similar conclusions where patients with TNBC had a significantly lower 3-year PFS and 3-year OS (p<0.001 for both) compared to non-TNBC.

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We believe that the poor survival and lack of new therapies for TNBC create a highly motivated group of patients who will rapidly adopt newly approved treatments.

Pricing for a new drug that addresses locally advanced or metastatic TNBC would likely be priced in line with recently approved agents for other forms of breast cancer. Pfizer’s (NYSE: PFE) *Ibrance* (palbociclib) is a cyclin-dependent kinase (CDK) inhibitor for hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER-2)-negative breast cancer and was first approved in February 2015. As shown in Figure 29, the wholesale acquisition cost (WAC) for a 28-day supply of *Ibrance* is $10,342, and the PFS in its Phase III PALOMA-3 trial was 9.5 months, which translates into roughly 10 treatment cycles and an annual treatment cost of $103,425 per patient. The total sales per patient for an approved drug to treat TNBC would depend on the duration of treatment, but this example provides a general estimate for pricing.

**Figure 29. Annual Cost of Ibrance for Breast Cancer**

<table>
<thead>
<tr>
<th>WAC Price Per Cycle of Ibrance</th>
<th>$10,342</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual Cycles Per Patient</td>
<td>10</td>
</tr>
<tr>
<td><strong>Annual Cost of Ibrance</strong></td>
<td>$103,425</td>
</tr>
</tbody>
</table>

*Source: LifeSci Capital*

We estimate that the total market opportunity for the treatment of TNBC patients exceeds $700 million per year in the US. This is based on 1) the assumption that 37,500 new cases of TNBC are diagnosed per year, 37% of which are locally advanced or metastatic, 2) that pricing per month would be equal to the cost of *Ibrance*, and 3) that the average cycles of treatment per patient would be 5.

**Advanced Ovarian Cancer Market.** The American Cancer Society estimates that 22,280 women in America will be diagnosed with ovarian cancer in 2016. Roughly 75% of patients will be diagnosed with Stage II, III, or IV disease and require systemic intervention such as chemotherapy, and as shown in Figure 30. Approximately 80% of patients will progress on available treatments. In total, there are an estimated 13,368 new cases of relapsed advanced ovarian cancer in the US and 27,000 cases in the EU per year.

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AstraZeneca’s Lynparza (olaparib) was approved in December of 2014 for patients with advanced ovarian cancer that have failed 3 or more lines of chemotherapy and who have BRCA mutations, which is estimated to be 15% of patients. 2015 sales of Lynparza totaled $94 million, and sales in the first quarter of 2016 were $44 million. Based on these sales and the current growth rate, full year 2016 sales are likely to exceed $200 million.

We estimate that the total market opportunity for the treatment of relapsed advanced ovarian cancer patients is $1.9 billion per year in the US and EU. This is based on 1) the assumption that 40,000 new cases of relapsed advanced ovarian cancer are diagnosed per year in these territories, 2) that pricing per month would be equal to the cost of Lynparza, which is $6,000 per month, and 3) that the average cycles of treatment per patient would be 8 based on the duration of response in studies with Lynparza.

Clinical Data Discussion for Supinoxin

Rexahn is conducting a Phase I clinical trial with Supinoxin to identify the recommended Phase II dose in cancer patients. No dose limiting toxicities have emerged at up to 775 mg once weekly. A new dosing schedule is being evaluated where patients receive 300 mg of Supinoxin 7 days per week. Identification of the recommended Phase II dose is expected in the second or third quarter of 2016, at which point Rexahn will begin enrolling patients with triple negative breast cancer and relapsed advanced ovarian cancer in a Phase Ib/IIa trial. Initial data from the Phase Ib/IIa are expected in the fourth quarter of 2016.

Ongoing Phase I Clinical Trial with Supinoxin in Cancer Patients

This is an open-label, dose-escalation Phase I clinical trial testing several doses of Supinoxin in patients with advanced or metastatic solid tumors. The starting dose of oral Supinoxin was 30 mg once weekly for 3 weeks followed by 1 week of rest. Up to 6 cycles were allowed. Patients were fasting at the point of Supinoxin administration. One patient is enrolled at the initial dose and evaluated for the emergence of a Grade 2 or above, treatment-related AE. If no related Grade 2 AE is observed, another patient is enrolled at the next dose. If a related Grade 2 AE emerges, then 3 patients will be enrolled at the next dose in a standard 3+3 fashion. The primary endpoint is safety, and secondary endpoints include pharmacokinetics and change in tumor size. Phosphorylated p68
via immunohistochemistry analysis will also be performed as an exploratory measure. The Company is also exploring and validating other potential predictive and pharmacodynamic biomarkers.

**Interim Phase I Results.** Rexahn presented interim data from the Phase I trial at the 2015 European Cancer Congress (ECC) in September 2015. The majority of AEs were mild and there was one case of moderate nausea. In terms of pharmacokinetics, there was largely a dose dependent increase in total drug exposure. The half-life averaged 14 hours. Rexahn was able to increase the dose of Supinoxin to 775 mg once weekly without the emergence of DLTs and used the PK data to model drug exposure using a more frequent dose schedule. The Company is currently treating patients in the trial with 300 mg of Supinoxin for 7 days per week, 3 weeks on and 1 week off per cycle.

There were initial signals of clinical activity in the Phase I trial. Four out of 12 evaluable patients experienced stable disease (SD). They represent 4 different tumor histologies and were treated with a suboptimal dosing schedule of Supinoxin. Three of the 4 patients with SD are still on therapy and Rexahn is also collecting data on phospho-p68 expression. This information could be valuable in later trials and could facilitate the development of a biomarker to select patients upfront who are more likely to benefit from Supinoxin.

**Planned Phase Ib/IIa Study**

Rexahn is planning to initiate a Phase Ib/IIa trial where it will explore the recommended Phase II dose of Supinoxin in patients with triple negative breast cancer and relapsed advanced ovarian cancer. Patients will be enrolled in two stages. Stage 1 will include 10 patients per cancer type. If there is sufficient clinical activity observed, another 40 patients will be enrolled. This will be determined independently for each cancer. Rexahn plans to initiate this trial in the third quarter of 2016 following the identification of a recommended Phase II dose. Interim data from the will be available as early as the fourth quarter of 2016. The 2016 European Society for Medical Oncology (ESMO) conference is one potential venue for these results.

**Intellectual Property & Licensing**

Rexahn Pharmaceuticals owns or has licenses to several US and international patents covering Supinoxin, RX-3117, and Archexin. Key patents have expected expirations between 2020 and 2030. Patents cover methods of use, synthesis, and composition of matter for Supinoxin, Archexin, and RX-3117. Additional patents related to Supinoxin, RX-3117, and Archexin are pending. In 2009, Rexahn acquired Supinoxin and all intellectual property related to quinoxaline-piperazine derivatives from Korea Research Institute of Chemical Technology (KRICT). They Company paid KRICT an initial licensing fee of $100,000, and will pay an additional $1 million following the first approval of a candidate from this agreement.

Rexahn entered into a research collaboration with Rexgene in 2003 to assist in the development of Archexin in Asia. Rexgene paid Rexahn a one-time fee of $1.5 million, and will pay a 3% royalty of net sales for licensed products related to Archexin in Asia. In addition, the Company has licensing agreements with the Ohio State University for an oligonucleotide drug delivery platform called Lipid-Coated Albumin Nanoparticle (LCAN), and the University of Maryland Baltimore for a drug delivery platform called Nano-Polymer-Drug Conjugate Systems. Rexahn will make payments to each institution based on developmental milestones achieved with these platforms.
Management Team

**Peter Suzdak, Ph.D.**  
*Chief Executive Officer*

Dr. Peter Suzdak joined Rexahn Pharmaceuticals in February 2013. Dr. Suzdak has over 25 years of diverse experience, including several management positions, in the pharmaceutical industry. Most recently, Dr. Suzdak was Chief Scientific Officer of Corridor Pharmaceuticals, a company developing small molecule compounds to treat pulmonary and vascular disorders. Prior to Corridor Pharmaceuticals, he was co-Founder, Chief Executive Officer and Chief Scientific Officer of Cardioxyl Pharmaceuticals, a company focused on therapies for the treatment of cardiovascular disease. Previous to Cardioxyl Pharmaceuticals, he was President and Chief Executive Officer of Artesian Therapeutics, a company engaged in the development of small molecule therapeutics for cardiovascular diseases. Dr. Suzdak’s experience also includes his position as Senior Vice President of Research and Development of Guilford Pharmaceuticals, a company that developed therapeutics and diagnostics for neurological diseases and cancer, and as Director of Neurobiology for Novo Nordisk. Dr. Suzdak holds a Ph.D. in pharmacology and toxicology from the University of Connecticut.

**Ely Benaim, M.D.**  
*Chief Medical Officer*

Ely Benaim, M.D. has more than 25 years of experience in healthcare including 15 years of clinical research experience in academia, government and pharmaceutical industry as well as extensive experience in global regulatory affairs. Dr. Benaim was most recently Senior Vice President of Regulatory Affairs & Chief Medical Officer of Berg Pharma. Prior to joining Berg Pharma, Dr. Benaim was Global Clinical Development Leader at Millennium/Takeda Pharmaceuticals where he oversaw global clinical development of the Aurora A kinase inhibitor program. Prior to joining Takeda in 2011, Dr. Benaim served as Vice President of Clinical Affairs for Sangamo BioSciences where he lead the development of zinc-fingers transcription factors cellular therapies in the areas of Cancer, Diabetes, Neurology, Cardiovascular and HIV. Before Sangamo, Dr. Benaim served at Amgen as Global Clinical Lead for the development of rilotumumab, a hepatocyte growth factor antibody for solid tumors, currently in late stage development. Prior to Amgen he was a Senior Director, Oncology Clinical Development at Salmedix/Cephalon Inc. (now Teva, Inc.) where he led the development of TREANDA® to a Phase 3 pivotal trial for lymphoma. Dr. Benaim received his M.D. from the Universidad Central de Venezuela, Caracas and completed his pediatric residency training at the University of South Florida. He completed fellowships in pediatric oncology and bone marrow transplantation at St. Jude’s Children’s Research Hospital, in Memphis, Tennessee. From 1997 to 2004, he was Assistant Professor in the Department of Pediatrics at the University of Tennessee and an Assistant Member to the Department of Hematology/Oncology. As a member of the Transplantation and Gene Therapy program he published several manuscripts on the areas of stem cell transplantation, immunology and gene therapy. Dr. Benaim also has a passion for global pediatric cancer awareness and care and has been awarded for his contributions in Latin America and the United States.

**Ted Jeong, D.Mgt.**  
*Senior Vice President & Chief Financial Officer*

Dr. Jeong has been Chief Financial Officer of Rexahn Pharmaceuticals since 2002. He oversees all aspects of capital raising, accounting, operations, and corporate development for Rexahn. He is also responsible for investor relations,
and played a key role in Rexahn’s 2008 listing on the New York Stock Exchange (NYSE) AMEX. For the past 20 years, he has extensive experience in venture capital and investment banking industry that includes role at Hyundai Venture Investment Corporation where he managed the Biotechnology investment team. Dr. Jeong holds a Doctor of Management from University of Maryland and an M.S. in Finance from Johns Hopkins University.

Reza Mazhari, Ph.D.
Vice President, Translational Medicine

Dr. Mazhari joined Rexahn Pharmaceuticals in June 2015. Dr Mazhari has more than 13 years of experience in various executive roles and therapeutic areas, successfully taking compounds from concept to clinic. Prior to joining Rexahn, he served as Vice President, Drug Discovery and Development at Cerecor Inc., a pharmaceutical company developing therapeutic agents for the treatment of neuropsychiatric disorders, from September 2011 through March 2015 and corporate Secretary from October 2011 through May 2013. Prior to joining Cerecor, Dr. Mazhari co-founded Cardioxyl Pharmaceuticals, Inc., a pharmaceutical company developing therapeutic agents for the treatment of cardiovascular disease, where he served as Vice President of Research and Pharmacology from October 2006 to September 2011. Dr. Mazhari is currently a part-time adjunct assistant professor of Medicine at the Johns Hopkins University. Dr. Mazhari received his B.S. and Ph.D. in Bioengineering from the University of California, San Diego.

Risk to an Investment

We consider an investment in Rexahn Pharmaceuticals to be a high-risk investment. Rexahn Pharmaceuticals is a development stage company with no history of taking a treatment to market and currently has no FDA approved drugs in its portfolio. The Company's clinical programs have not yet entered Phase III trials and have generated limited data to date. Furthermore, early indications of efficacy do not necessarily translate into positive late-stage results. Phase III clinical trials will result in significant additional expenses to the Company and may require additional rounds of dilutive financing. As with any company, Rexahn Pharmaceuticals may be unable to obtain sufficient capital to fund planned development programs. There are regulatory risks associated with the development of any drug and Rexahn Pharmaceuticals may not receive FDA approval for its candidates despite significant time and financial investments. Regulatory approval to market and sell a drug does not guarantee that the drug will penetrate the market, and sales may not meet expectations.
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