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INDUSTRY UPDATE NOTE

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Sector Analysis Update: Rare Diseases/Neuro-oncology Companies at AACR

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This week a number of companies in our Rare Diseases and Comparative Biology/Vet Biotech subsectors are presenting data at the American Association for Cancer Research Annual meeting being held in New Orleans. The AACR was founded in 1907 and is the premier professional organization focused on cancer research. Many companies use the AACR as the launching point for announcing new therapeutic paradigms, such as CAR-T, checkpoint inhibitors or cancer microenvironment immunomodulation, as well as to release significant preclinical and early clinical data. Other seminal academic meetings occurring this time of year include the American Society of Gene & Cell Therapy (ASGCT) annual meeting in early May and the American Society of Clinical Oncology (ASCO) in June. Together, investor response to data presented at this trio of research meetings often signals both where the next "technology" opportunity is and what technical issues are surfacing with prior years' "hot" therapeutic approaches. As such, these meetings are highly scrutinized by investors and are often bellwethers for investor sector appetite or disdain. Based on discussions at cancer immunotherapy meetings earlier this year, we expect to hear several new buzzwords such as progressive combination therapy, tumor microenvironment mediation, neo-antigen priming, next-gen sequencing of tumors.

As was the case with last year's initial disappointments related to the use of CAR-T (chimeric antigen receptor-modified T cells) for treating solid tumors, this year may see surfacing concerns with checkpoint inhibitors (CPIs), which could substantially cool investor interest in the class. CPIs block a class of molecules found on selected immune cells that need to be activated or inactivated to promote an immune response. Cancer cells have been found to mediate these checkpoint molecules to evade normal immune response. The most notable of these checkpoint molecules is PD-1. Through interaction with its sister molecule, PD-L1, a checkpoint protein found on T-cells, the complex acts as an "off-switch" for T-cells and prevents an immune response. Large amounts of PD-L1 are found in a number of cancer cells and significantly contribute to cancer immune evasion. **Keytruda**® and **Opdivo**® are the first commercialized anti PD-1 therapies on the market, and thanks to their outstanding success for certain patients, checkpoint inhibitors gained celebrity status during 2015. Like CAR-T, which is now proving rather narrowly effective with only very limited success outside of AML, this year we expect AACR discussion to begin to address a major short-coming of checkpoint inhibitors—their effectiveness in a narrow patient population and difficulty in determining those responders. To that end, companies are looking at the tumor microenvironment for genetic clues for patient stratification and manipulation of the tumor microenvironment to potentiate immune therapies. Almost universally, the strategy du jour is partnered combination therapies, i.e., standard of care + checkpoint inhibitors or CPIs + immune therapy. In fact, Merck (MRK-$56.86-Not rated) and AstraZeneca (AZN-$30.25-Not rated) in particular, have become the leaders in combination therapy partnerships with biotechs in immune-oncology.

Please find Important Disclosures beginning on Page 6.

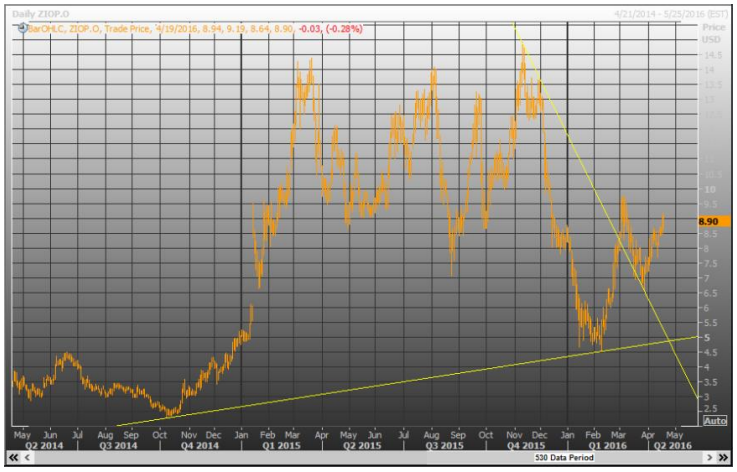
We would like to take this opportunity to highlight several companies who are specifically releasing data at the AACR and upcoming ASGCT meetings:

Advaxis (ADXS-$9.42-Not rated)—In its simplest form, Advaxis's core technology seeks to drive T-cell response against cancer cells by promoting cancer antigen-specific cytotoxic T-cell activation while changing the tumor microenvironment by reducing the influence of T-regulatory cells, which can be a source of cancer immunity. Data on Advaxis' HPV-specific immunotherapy candidate, AXAL, was presented in a late-breaking poster detailing a physician-sponsored Phase II trial of head and neck cancer patients. The data indicate that AXAL antigen-specific activated T-cells were able to infiltrate tumors and possibly favorably condition the tumor microenvironment towards cytotoxic T-cell response. The conditioning of the microenvironment is viewed as a positive for CPI's and Advaxis is pursuing checkpoint inhibitor combination therapies with Merck, AstraZeneca and Incyte (INCY-$76.77-Not rated). The Company recently gave updates on the AstraZeneca and Merck checkpoint inhibitors + Advaxis drug combinations, both of which are progressing through dose escalation.

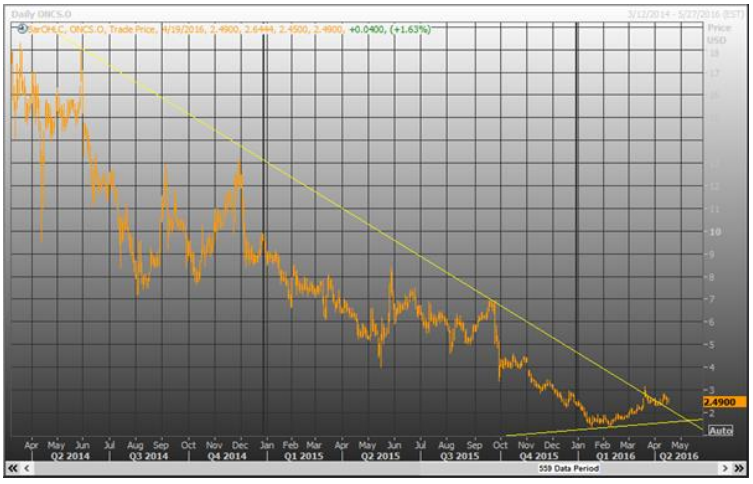
In addition to interim data from its Phase I/II clinical trial in glioblastoma (GBM), **Del Mar Pharmaceuticals Inc.** (DMPI-$1.33-Not rated) presented data at the "*New Mechanisms of Anticancer Drug Action*" session of AACR on the molecular mechanism of action for VAL-083 (dianhydrogalactitol). Interestingly, although dianhydrogalactitol has a long scientific history and has been studied in over 40 NCI-backed Phase I and Phase II trials, it was not until fairly recently that advances in research tools have permitted the study of its underlying mechanism of action. Because VAL-083, an alkylating agent, acts independently of the MGMT resistance mechanism of other anti-cancer alkylating agents, it has been thought that VAL-083 had a second mode of action that enables the drug to still be effective where other alkylating agents such as temozolomide (Temodar), are not. Del Mar's poster describes VAL-083's activity in causing durable DNA interstrand crosslinks that result in the cell's DNA to sustain irreparable double-strand breaks. In turn, this causes cell cycle arrest at a key cell division phase and drives the cell into apoptosis. It is postulated that cancer cells lack normal cell cycle check-points and DNA repair mechanisms and thus are unable to stop the process by which these DNA damaging crosslinks lead to cell apoptosis.

Ziopharm Oncology Inc. (ZIOP-$8.88-Not rated) is developing several cell-based technologies for the treatment of cancer and auto-immune diseases such as graft vs host disease (GvHD). Its cell-based programs leverage a collaboration with Intrexon (XON-$35.76-Not rated) and MD Anderson Cancer Center and combine T-cell based approaches such as CAR-T and TCR (T-cell receptor modified T-cells) with in situ gene

transfer/activation to generate both autologous and allogeneic cell-based products. Ziopharm's most advanced program is a 'switch-on in situ" gene activated intratumoral IL-12 treatment, Ad-RTS-mIL-12, for breast cancer, now in Phase II trials. The same delivery and gene activation technology based on Intrexon's Rheoswitch ®, is incorporated into a Phase I trial for GBM. Ziopharm will be presenting data in oral sessions at the American Society of Gene & Cell Therapy Annual meeting on May 6th related to this novel gene controlled expression of IL-12 in combination with a PD-1 inhibitor aimed at treating GBM. Ziopharm last reported data on its GBM program at the Society of NeuroOncology meeting last November, which demonstrated its "switch-on" gene therapy can deliver intratumorally produced IL-12 and activate the innate immune system. IL-12 is a pro-inflammatory cytokine that can reverse some immune escape mechanisms, thus improving the functionality of activated CD8+ T-cells (cytotoxic T-cells). However, exogenously delivered IL-12 has a poor safety record and its therapeutic use has been hampered by its very high side effect profile.

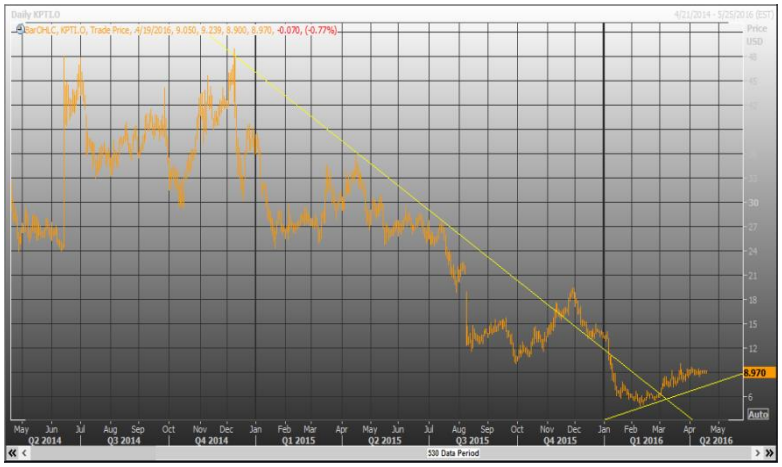


Also seeking to find a suitable delivery system for IL-12 is **OncoSec Medical** (ONCS-$2.41-Not rated). OncoSec is pursuing an electroporation delivery system for plasmid IL-12 and has completed a Phase II clinical study using electroporation delivery of IL-12 as a monotherapy in patients with advanced melanoma. A selected group of these melanoma patients went on to receive anti-PD1/PD-L1 therapy. The abstract "*Intratumoral electroporation of plasmid IL-12 can prime response to anti-PD1-PD-L1 blockade in patients with Stage III/Iv-M1a melanoma*" was published over the weekend in the ***2016 AACR Annual Meeting Proceedings*** and indicated that OncoSec's ImmunoPulse™ IL-12 can prime these patients for the added benefit of checkpoint inhibitors against PD-1 and PD-L1. The data showed 64% of patients demonstrated a complete or partial immune-related response to the add-on checkpoint inhibitor therapy. This result compared to a 31% overall response rate in ONCS's prior Phase II melanoma monotherapy trial. ONCS is already in a collaboration with Merck for a melanoma combination therapy with ImmunoPulse IL-12 in **Keytruda** non-responders.

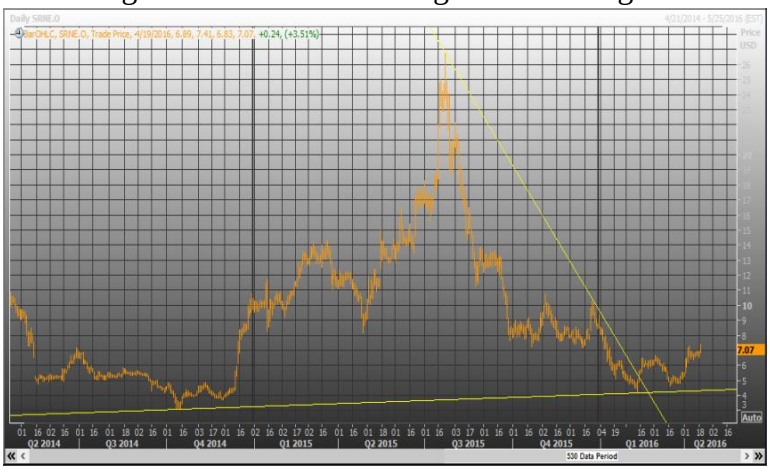


In a different version of the combination therapy biotech partnership, OncoSec has formed a collaboration with Heat Biologics (HTBX-$0.68-Not rated) to enhance the delivery of tumor-associated antigens intratumorally via DNA electroporation. The companies presented the poster, "*In vivo intra-tumoral electroporation of Gp96-Ig/Fc-OX40L stimulates CD8+ T cell cross-priming tumor specific neoantig*ens", which detailed preclinical data from studies using OncoSec's electroporation technology to augment Heat Biologics' ***ComPACT*** Gp96-Ig and Fc-OX40L antigen presentation technology in an attempt to enable tumor neo-antigen secretion from individual patient tumors as a new methodology for immunotherapy.

Karyopharm Therapeutics Inc. (KPTI-$9.04-Not rated) is using the AACR to not only announce recent data related to its lead product, selinexor (KPT-330), but also to describe a broad body of preclinical research that highlights key findings from its oncology pipeline and lends support for KPT-300's potential importance as a backbone therapy in combination with a variety of other immune-oncology and anti-cancer agents across both hematological and solid tumors. Among the 19 poster presentations is data from two clinical candidates beyond selinexor, KPT-8602 and KPT-9274. KPT 8602 is a second generation oral SINE (Selective Inhibitor of Nuclear Export) compound that has just entered the clinic. Both KPT330 and KPT8602 target the blocking of a key nuclear export protein, XPO1, which is instrumental is transporting tumor suppressor proteins out of the cancer cell nucleus. Preventing this transport mechanism allows for the normal selective elimination of genomically damaged or neoplastic cells. KPT-9274 is a first-in-class orally bioavailable small molecule dual acting anti-tumor agent that exerts effect through energy depletion and eventually, leads to apoptosis. The KPT-9274 compound will be entering the clinic later this year. Data supporting the utility of SINE compounds in triple negative breast cancer, neuroblastoma and in use in combination with checkpoint inhibitors is reported among the remaining 17 posters.



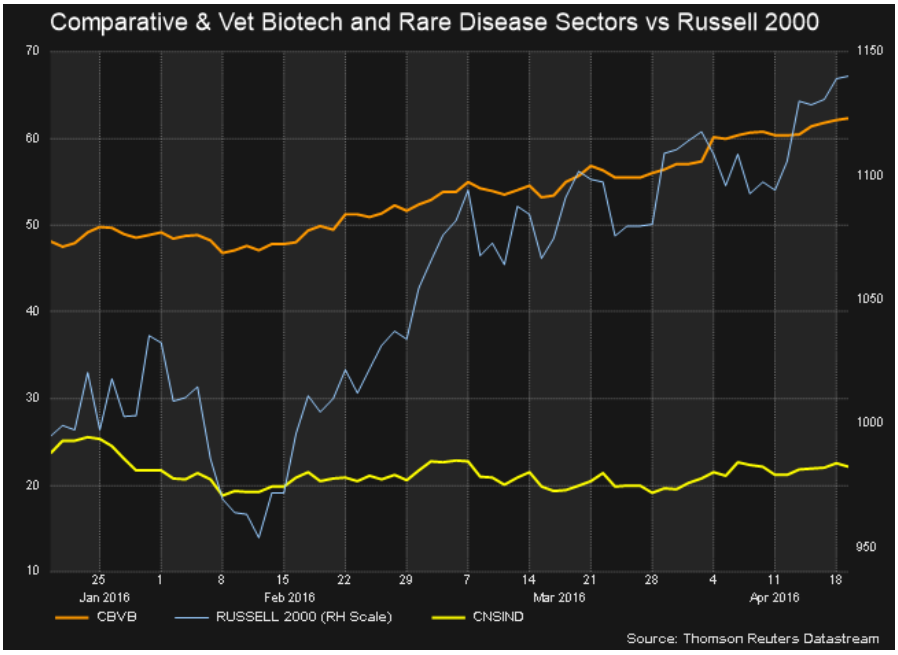
Sorrento Therapeutics (SRNE-$7.11-Not rated) which is closing a $150 million financing with its South Korean partner, Yuhan Corporation and Ally Bridge Group as leads, is perhaps a premier example of the "targeted combination" therapy. The Company is advancing a number of technologies combining immune-oncology with cellular based therapies and antibody drug conjugates. The company has both receptor and checkpoint inhibitor targeting monoclonal antibody programs and CAR-T cell therapeutics in numerous clinical trials. In separate abstracts at this year's AACR, Sorrento presented new in vitro mechanism of action data related to its back pipeline including data on an anti-5T4 antibody drug conjugate ZV05, which is a chemotherapeutic targeting and potentiator agent and its anti-TIM3 checkpoint inhibitor programs. A third abstract gave new data on Sorrento's novel antibody drug conjugate for non-small cell lung cancer.



Closing Thought: Judging from recent comments from leading researchers at MD Anderson, the NIH, Memorial Sloan Kettering, Mass. General and others who spoke at William Blair's Cancer Immunotherapy conference in March, we appear to be entering a new era in cancer treatment, built on collaboration and the leveraging of combination strategies. Treatment goals are also shifting and moving away from focus on just primary disease to obtaining a far better understanding of individual disease progression and its impact on the prevention or management of metastasis, which is in fact, what results in death. We expect to hear exciting news from the AACR and the other upcoming medical meetings about advancement in the new technologies and approaches being explored by the companies we've highlighted in this Update and others in the sector. *SG*

DAWSON JAMES COMPARATIVE BIO & CNS/RARE DISEASE SUBSECTORS VS RUSSELL 2000

Year to Date Performance



52 Week Performance

Note: All Charts courtesy of Thomson Reuters Datastream

Risk Factors

In addition to normal economic and market risk factors that impact most equities, and the common risks shared by the companies named in this sector and those in the biotechnology sector as a whole, we believe an investment in any of the Dawson James CNS Rare Disease Sector companies involves the following risks:

- **Regulatory risks** – the companies in the DJ CNS Rare Disease Sector are subject to regulatory review for their ongoing research and development activities and manufacturing operations with local, state and federal governmental agencies both in the US and Internationally.

- **Need to defend patents, trade secrets and other intellectual property** – Biotechnology companies rely heavily on intellectual property related to their technology and products. While larger companies may have adequate resources to defend their intellectual property, most of the smaller companies in the DJ CNS Rare Disease Sector would be materially and negatively impacted by intellectual property infringement or the loss of one or more patents.

- **Historical lack of profitability** – To date this year and in past years, most of the companies in the DJ CNS Rare Disease Sector have not operated on a profitable basis, and are not forecast to do so in the immediate future. Although companies typically have been able to raise funds from the capital markets, there can be no guarantee that any particular company will not be able raise additional operating capital in the future should losses continue.

- **Competitive Markets** – This universe of companies operate in a highly competitive marketplace, where speed to market, clinical results and other factors bear on a company's viability. There can be no assurance that any one company will be able to continue to market or later launch its products successfully in these competitive markets in the future.

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2) **Neutra**l: the analyst believes the price of the stock is fairly valued for the next 12-18 months;
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Ratings Distribution	# of Companies	% of Total	# of Companies	% of Totals
Market Outperform (Buy)	16	67%	10	63%
Market Perform (Neutral)	8	33%	6	75%
Market Underperform (Sell)	0	0%	0	0%
Total	24	100%	16	67%

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