MTSL Issue 912

October 4, 2019

UPDATES: FPRX, INCY, MDCO, NKTR, SGMO, ZIOP, ZIOP

IN THIS ISSUE: Political Fears Dominate HC/Biotech Stock Performance

Since Last Issue: BTK: -5.3%; NBI: -5.5%; XBI: -7.2%; Model Portfolio: -7.8%; Trader's Portfolio: -20.0%

BIOTECH SECTOR ANALYSIS

SENTIMENT — Warren & Trump & Impeachment, Oh My!

There is no doubt that fund managers have decided to wait out the enhanced volatility and negativity with regard to drug price controls and the upcoming (but still a year+ away) Presidential election. Throw in the overall market correction due to a slowing global economy, and very high beta biotech stocks have become sources of funds. Looking at the poor XBI chart below, we can feel good about our MDCO recommendation in an otherwise awful six months for small biotechs. The same, however, cannot be said about the majority of stocks in our universe (except ACAD), but we strongly believe that fundamentals are intact and/or improving for these companies and that their respective times back in the spotlight will eventually return. When it comes down to it, developing and commercializing successful new drugs that exceed consensus expectations is what drives

Dr. Stephen Hahn is rumored to be the next commissioner of the FDA. Hahn is a radiation oncologist and Chief of the MD Anderson Cancer Center. With all of the activity and progress occurring in immuno-oncology, Hahn would be a strong pick for many biotech (and pharma) companies focusing on the burgeoning field. As a reminder, MD Anderson is a key institution for MTSL Recommendation ZIOP – it is where CEO Laurence Cooper was at since 2008. Moreover, the Company licensed its CAR-T technology from the research institution. Furthermore, it is where ZIOP's latest third-generation CAR-T clinical trial is about to start (https://clinicaltrials.gov/ct2/show/NCT03579888?term=Ziopharm+M.D.+Anderson&rank=2).

M&A – DOVA/SOBI Another Nice Premium

Dova Pharmaceuticals (DOVA) has agreed to be acquired by Swedish Orphan Biovitrum AB (Sobi) for $27.50 per share, along with a CVR that entitles holders of DOVA to an additional $1.50 per share upon regulatory approval of DOPTELET for the treatment of chemotherapy-induced

stock prices but in the current market such progress if and when it occurs is often used as a reason to sell. Granted, there are way too many little companies all saying the same things and separating the wheat from the chaff is no easy task, but that is what we do at MTSL.

For now, the charts have broken down everywhere and there has not been a lot of good sector news since ACAD's HORIZON trial early halt, and that was only 2-3 weeks ago but seems like forever. The latest KRAS data fell short of expectations and that is from an industry leader (AMGN) so the impact is wider than that of a small cap name. There is still a lot of cash on most balance sheets and that helps the runways, but that is not why people invest in the sector – novel new value-added drugs with exceptional late-stage data like Inclisiran are. But for now, the MDCOs are few and far between. The overall market fears, declining global economy and a possible Elizabeth Warren Presidency has investors in a risk off mode, and that keeps biotech stocks out of favor.

Warren Is Surging And She Wants Medicare For All

Whether or not we are liberals at heart, the polls are telling us that Elizabeth Warren is heading in the direction of the Democratic nominee for 2020. We are still several months away from a final candidate and next year's election, but the impeachment procedure in our view is pushing Warren even farther and faster

thrombocytopenia (CIT). The price reflects a solid premium of 36% to Dova's closing price on September 27, and a 59% premium to the 30-day average price. While not a blockbuster deal, the DOVA/SOBI deal is a good sign that despite poor stock activity and drug pricing fears, premium takeover deals are still in the works.

FINANCE – Closing Time?

Yes, last Issue we praised the success of some new biotech IPOs – IGM Biosciences (IGMS) in particular. Over the past few weeks, unfortunately, the market's appetite for new companies has rightfully come to an understandable slowdown. Nonetheless, bankers are relentless and companies insatiable and deals can and may still get done, whether at a discount or not.

Some IPOs can get done, despite the market's resistance to risk overall. This past week, at least a handful got through while others did not. ADC Therapeutics, another one-time unicorn, pulled its IPO the day before pricing due to market conditions. Frequency Therapeutics (FREQ) raised ~$84 million at 14, and closed just below deal price. That small deal was done by Wall Street powerhouses JPMorgan, Goldman Sachs and Cowen. One successful deal was Viela Bio (VIE), which priced at 19 and currently trades around 23. Viela is a bit unique that it is a spinoff of MedImmune/AZN, which owns 38% of the Company. Finally, Aprea Therapeutics (APRE) is another early trading winner, priced at 15 and is now trading at 19. More are on the way, with unicorns BioNTech and Vir, looking to try the IPO market this week. Hence, the public markets may be under duress, but there is surprisingly major activity in the new issues, where VCs and large dedicated funds have vested interests.

CALENDAR/KEY EVENTS – MRTX/AMRN/SRPT Catalysts; WMS Underway and SITC/AHA Next Big Med Conferences

to the top of the list and the market is taking notice. Bernie Sanders' latest heart surgery cannot be good for his chances either (although he may physically feel stronger after clearing the blockages). Warren's "Medicare for All" call could lead to important changes in drug pricing and that is not what biopharmaceutical investors (nor generalists) want to hear. (Although it may actually also lead to more patients getting treated over time.) Good new drugs will get used and paid for (e.g., Inclisiran, Ocrevus, Spinraza, etc.), but uncertainty continues to rise with both global trade wars and undecided health care policy that for now is keeping buyers on the sidelines and sellers dropping bids. At press time, Trump announced another executive order "protecting" Americans from Democrats' "Medicare for All" proposals. It may be what gave the biotech market a small bounce, but soaring health care costs are very real and bears/shorts know that for now, time is on their side.

Technicals – Oversold Bounce But The Damage Is Done

Biotech fund flows have been negative for 6+ weeks now – and flows are probably the greatest, single non-fundamental variable for stock performance. The technicals look horrendous and the XBI officially touched oversold territory before a little bounce at press time. Last Issue, it looked like we were close to breaking out but the impeachment quickly reversed any such optimism. The XBI not only didn't rise above the moving averages, but it actually broke the 200-WEEK MA (see XBI weekly below). Closing at 76, the index is now below the 50-WEEK and sitting on the 200-WEEK moving average, having just bounced off of oversold levels with the RSI at 37 (just was 29). The MACD has also declined again, closing at recent lows (see XBI daily above).

With ESMO (oncology) behind us, investors will focus on the WMS (muscle diseases like SMA) meeting this weekend and ESGCT (gene therapy) in October and bigger meetings like the SITC and AHA conference in early-to-mid November. Some of the recent "stock winners that have turned into losers" – MRTX, AMRN, SRPT – are due for important clinical/regulatory catalysts at these meetings and/or over the next 1-2 months. SRPT will show its recent LGMD 2E 9 month functional data at the WMS on Friday (10/5). MRTX will release initial data of its KRAS inhibitor and AMG510 competitor, MRTX849, on October 28, while AMRN will hear the FDA's concerns in deciding Vascepa's label expansion (November 12 release of briefing documents; AdCom November 14). Consensus expectations for all three have come in dramatically for the right reasons (CRL SRPT, AMGN's softening KRAS results and AMRN's unexpected AdCom panel). All three events will bring massive volatility and any unexpected good news might boost the respective stocks and maybe the group.

After two strong Phase III winners of late in MDCO and ACAD, we highlight upcoming events for additional MTSL Recommendations including ALKS, BMRN, MDGL, INCY, IONS, SGMO and ZIOP. Busy season will get busier and let's see the pendulum swing back into favor for a handful of these stocks. (Click on the table to get a larger read of the calendar.)

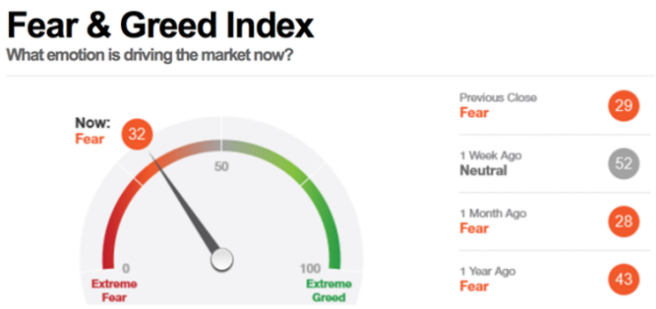
October/November Biotech Events - Scientific & Investor

Date	Host	Event	Location
9/27-10/1	ESMO	European Society for Medical Oncology	Barcelona
10/1-5	WMS	World Muscle Society Annual Meeting	Copenhagen
10/2-6	ID Week	Infectious Disease Week	Washington DC
10/2-4	Alliance for Reg. Med.	Cell & Gene Meeting On The Mesa	Carlsbad
10/7	Charden	Genetic Medicine Conference	New York
10/22-25	ESGCT	European Society for Cell & Gene Therapy	Barcelona
10/22-23	BIO	Investor Forum	San Francisco
10/25-30	ACG	American College of Gastroenterology	San Antonio
10/31-11/2	CF Foundation	North American Cystic Fibrosis Conference	Nashville
11/6-10	SITC	Annual Meeting	Maryland
11/16-19	AHA	Annual Meeting	Philadelphia

Acadia (ACAD)

The XBI entire year's gain has been wiped out. The last time the XBI weekly broke the 200-week MA was in December during a market meltdown, as we write (Thursday) it bounced to hold that key support. Recent winners have been decimated (e.g., SRPT, BLUE, GWPH), and have a long way to come back even with positive news. The sentiment is terrible. Stock picking is critical and even being right may not be enough for the time being. There really has not been a lot of very bad news, but the overriding geopolitic and POTUS election has too many investors reminded of the infamous "Hillary Tweet" of September 2015. October is a spooky month which is known for market crashes, and the same sell off occurred this time last year (see XBI weekly above).

After hitting a ~65 GREED index level since last Issue, the Fear and Greed Index has pulled back precipitously to 32 – again in the FEAR zone. We are not exactly sure what the biotech F&G index is but by the sentiment and stock price performance, it is probably lying in EXTREME FEAR now.



- Nuplazid HARMONY trial in Dementia-Related Psychosis (DRP) –late breaking oral presentation of the positive top line release to be presented at the 12th Clinical Trials on Alzheimer's Disease (CTAD) Meeting, December 4-7, 2019 in San Diego, California.

Alkermes (ALKS)

- PDUFA for VUMERITY (BIIB-098) in MS – Q4:19

BioMarin (BMRN)

- Phase III data for vosoritide (achondroplasia) – YE:19/Q1:20
- BLA filing for ValRox in the U.S. – by year-end

Ionis (IONS)

- Spinraza data update at WMS Annual Meeting **(October 1-6)**
- Huntington's disease data for RG6042 from partner Roche YE:19

Incyte (INCY)

- File NDA for pemigatinib by YE:19

Nektar (NKTR)

- IL-2 combos – Initial Phase I data – YE:19
- 5 abstracts at SITC including updated data from the PIVOT-02 study of bempegaldesleukin (NKTR-214) with nivolumab in first-line metastatic melanoma **(Nov. 6)**

The Medicines Company (MDCO)

- Inclisiran Phase III ORION 9 and 10 study full presentations are due at AHA in **November**
- File Inclisiran BLA in the U.S. (YE:19)

DATA – MDCO Hits Paydirt Again, AMGN's KRAS Disappoints In CRC

The ORION 9 and 10 trials followed the successful path of the first Phase III trial released earlier this month, ORION 11 (see MDCO below). That has kept MDCO shares standing alone near 52-week highs. But AMGN released further AMG 510 results, this time in patients with colorectal cancer. The data showed that only 1 of 29 patients exhibited a partial response. The lower-than-expected data also hit shares of Mirati (MRTX). Mirati is developing its own KRAS G12C inhibitor, MRTX849, with data due later this year and until now has been riding the success of '510. As we said in the last Issue, the bloom is off the KRAS rose.

REGULATORY – GILD HIV Prevention; New FDA Chair – Good for ZIOP?

The FDA approved a pre-exposure prophylaxis (PrEP) indication for GILD's Descovy (emtricitabine 200 mg and tenofovir alafenamide 25 mg tablets; F/TAF). Descovy for PrEP™ is indicated to reduce the risk of sexually acquired HIV-1 infection in adults and adolescents weighing at least 35 kg who are HIV-negative and at-risk for sexually acquired HIV, excluding individuals at-risk from receptive vaginal sex.

Sangamo (SGMO)

- Cell & Gene Meeting on the Mesa **(Oct. 2-4)**
- SB-525 – hemophilia A Phase II update at ASH (Q4)
- SB-920 STAAR – first patient enrollment in Fabry's disease – YE:19
- ST-400 – additional preliminary data (Q4) in beta-thal
- TX-200 – initiate Phase I/II trial in solid organ transplant (RCC)

Ziopharm (ZIOP)

- Initiation of human trials for its novel TCR program – **October**
- Phase 1 clinical trial of CD19-specific CAR-T, produced using a process termed rapid personalized manufacture (RPM) via Sleeping Beauty, for patients with relapsed CD19+ leukemias and lymphomas – before YE:19

Clinical Trials Watch

Relevant New Studies or Changes Posted on ClinicalTrials.gov for our MTSL Portfolio and/or Related Companies S

ABBV – A Study of the Safety and Efficacy of Risankizumab in Adult Participants With Plaque Psoriasis Who H Secukinumab or Ixekizumab

AMGN/CELG – Study of Daratumumab Combined With Carfilzomib, Lenalidomide and Dexamethasone for N

Baylor College of Medicine – C7R-GD2.CAR T Cells for Patients With GD2-expressing Brain Tumors (GAIL-B)

CELG – Pharmacogenetics Sampling of the CC-90007-CP-003 Study Cohort

CELG – Validation of the PsASon ULtrasound Scores in Patients With Psoriatic Arthritis Undergoing TReatme

HRTX – Extended Delivery of Bupivacaine Study in Herniorrhaphy

INCY – Platform Study of Novel Ruxolitinib Combinations in Myelofibrosis Patients (ADORE)

New York Medical College – AlloSCT for Malignant and Non-malignant Hematologic Diseases Utilizing Alpha Depletion

ZIOP/NCI – Non-Viral TCR Gene Therapy

Company Updates

UPDATES: FPRX, INCY, MDCO, NKTR, SGMO, ZIOP, ZIOP

FPRX – Presents Updated FPA150 Data at ESMO

FPRX presented updated data from the Phase 1a/1b clinical trial of FPA150 in patients with advanced solid tumors in a poster presentation at the European Society for Medical Oncology (ESMO) meeting. The FPA150 data presented at ESMO included preliminary efficacy results from the Phase 1b monotherapy expansion portion of the study in patients preselected for B7-H4 tumor overexpression across breast, endometrial and ovarian cancers, and early safety results from the Phase 1a Keytruda® (pembrolizumab, a PD1 antibody) combination portion of the study in patients preselected for B7-H4 tumor overexpression in ovarian cancer.

Key highlights from the presentation include:

Phase 1 FPA150 Monotherapy:

Phase 1 Safety Lead-in Combination of FPA150 + Pembrolizumab :

- Combination was well tolerated in the first four patients treated with FPA150 (20 mg/kg) and pembrolizumab (200 mg)
- Expansion initiated in August 2019 in a cohort of ovarian cancer patients with B7-H4 overexpression

The data is solid and interesting, particularly the ability to work in combo with PD-1 inhibitors. That being said, the data is both early and a small sample explaining why it had no effect on the stock in the current risk averse environment for small bios. FPRX' stock remains under pressure as the recent management shakeup leaves the Company with few supporters and in a "prove it" stage from Wall Street's

- Two patients with B7-H4 positive ovarian cancer experienced a confirmed partial response (one in the dose escalation and one at the recommended dose of 20mg/kg)
- 10 patients with stable disease remain on therapy as of August 9, 2019
- Increased tumor infiltration of T cells and NK cells observed in patients with a partial response or stable disease
- Recommended dose of 20 mg/kg was well tolerated in all patients

point of view. Given the stock's significant pull back we are reducing our BUY to 8 (from 20) and our TARGET to 16 (from 30).

RECOMMENDATION

FPRX is a BUY under 8 with a TARGET PRICE of 16

INCY – Presents Strong Data for Pemigatinib at ESMO, Will File NDA by Year End

Maintaining its novel compound excellence, INCY recently presented strong data from the pivotal FIGHT-202 trial of pemigatinib in r/r cholangiocarcinoma at the European Society for Medical Oncology (ESMO) meeting. Pemigatinib demonstrated an objective response rate (ORR) of 35.5% in r/r cholangiocarcinoma patients with FGFR2 fusions/rearrangements with a generally well-tolerated safety profile consistent with prior datasets. These data are expected to form the basis for a NDA filing by YE19 under the granted Breakthrough Therapy Designation (BTD), though we note that cholangiocarcinoma is a relatively small opportunity.

While the initial market is relatively small (-~2,000-3,000 annually), many more patients overexpress the FGFR2 biomarker. INCY has a broad clinical development program underway to expand the pemigatinib opportunity. The Company has already initiated the pivotal trial of pemigatinib in 1L cholangiocarcinoma vs. chemo.

INCY is also expanding pemigatinib in bladder cancer with FGFR3 mutations or fusions/rearrangements. The FIGHT-205 trial is being initiated to evaluate pemigatinib vs. standard of care in frontline bladder cancer patients expressing FGFR3 mutations or fusions/rearrangements. INCY has also opened a tumor agnostic trial (FIGHT-207) to explore pemigatinib in different solid tumors with FGFR alterations.

RECOMMENDATION

INCY is a BUY under 75 with a TARGET PRICE of 95

MDCO – (9/25/19) ORION 9 & 10 Complete The Inclisiran Trifecta

We reiterate our BUY of MDCO shares after the successful completion of the ORION LDL Lowering clinical program. Along with ACAD, two of the top biotech Phase III trials of 2019 are MTSL recommendations that are driving investors back to biotech – REITERATE BUY

Efficacy & Safety "At Least As Favorable As ORION-11" – Positive topline results for the **ORION-9 Phase 3 clinical study in patients with Heterozygous Familial Hypercholesterolemia (HeFH).** ORION-9 met all primary and secondary endpoints, and inclisiran demonstrated durable and potent efficacy and was well-tolerated with excellent safety that was generally well-balanced between the treatment groups. *Most importantly, there were no treatment-related liver or renal laboratory abnormalities.*

Positive topline results for the **ORION-10 Phase 3 clinical study in patients with atherosclerotic cardiovascular disease (ASCVD), successfully completed the pivotal Phase 3 LDL-cholesterol (LDL-C) lowering clinical trials for inclisiran.** ORION-10 met all primary and secondary endpoints, and inclisiran demonstrated efficacy, tolerability and safety that were at least as favorable as observed in ORION-11, *once again there were no treatment-related liver or renal laboratory abnormalities.*

Detailed efficacy, tolerability and safety data from ORION-9 and ORION-10 will be presented at the American Heart Association (AHA) Scientific Sessions in Philadelphia on **Monday, November 18**, 9:24am EST, during *Late Breaking Science VI: New Frontiers in Lipid Therapy.* The company will also present data from the ORION-10 study in ASCVD patients at the AHA

ORION-10 is a pivotal Phase III, placebo-controlled, double-blind, randomized study to evaluate the efficacy, safety and tolerability of inclisiran sodium 300 mg administered subcutaneously in 1,561 participants with ASCVD and elevated LDL-C, despite maximum tolerated dose of LDL-C-lowering therapies (e.g., a statin or ezetimibe). The primary endpoints are percentage change in LDL-C from baseline to day 510 (17 months) and time-adjusted percentage change in LDL-C from baseline after day 90 (three months) and up to day 540 (18 months). The majority of study participants are taking inclisiran or placebo in addition to existing lipid-lowering therapy with a maximally tolerated statin (with or without ezetimibe). Key secondary endpoints include the mean absolute change at Day 510 (17 months), the average absolute reduction from Day 90 (three months) up to Day 540 (18 months), and changes in other lipids and lipoproteins. The study was conducted at 145 sites in the United States. Each study participant received inclisiran sodium 300 mg administered as a subcutaneous injection initially, again at three months and then every six months thereafter. The majority of study participants are taking inclisiran or placebo in addition to existing lipid-lowering therapy with a maximally tolerated statin (with or without ezetimibe).

Takeout Potential Continues To Rise

The ORION Phase III clinical trial program (ORION 9, 10 and 11) paves the way for FDA approval, market expansion and eventual commercial dominance. Once again, Inclisiran provides patients and physicians with a safe, effective and extremely user friendly and affordable protocol to reduce LDL cholesterol compared with any other option available today. Upcoming events include the AHA presentations

congress on Saturday, **November 16,** 11:06 am EST, during Late Breaking Science I: Outside the Box: New Approaches to CVD Risk Reduction.

Design Of Both Trials

ORION-9 is a pivotal Phase III, placebo-controlled, double-blind, randomized study to evaluate the efficacy, safety and tolerability of inclisiran sodium 300 mg administered subcutaneously in 482 patients with clinical or genetic evidence of HeFH and elevated LDL-C, despite maximum tolerated dose of LDL-C-lowering therapies (e.g., a statin or ezetimibe). The primary endpoints are percentage change in LDL-C from baseline to day 510 (17 months) and time-adjusted percentage change in LDL-C from baseline between day 90 (three months) and up to day 540 (18 months). Key secondary endpoints include the mean absolute change at Day 510 (17 months), the average absolute reduction from Day 90 (three months) up to Day 540 (18 months), and changes in other lipids and lipoproteins. The international study was conducted at 54 sites in eight countries. Each study participant received inclisiran sodium 300 mg administered as a subcutaneous injection initially, again at three months and then every six months thereafter. The majority of study participants are taking inclisiran or placebo in addition to existing lipid-lowering therapy with a maximally tolerated statin (with or without ezetimibe).

(November), BLA and EU regulatory filings (Q4:19, Q1:20, respectively). The ORION 11 data was better than the top-line summary and we expect that the details of ORION-9 and ORION-10 will follow suit. In our view, inclisiran is almost completely de-risked with over 3,000 patients treated for as long as three years, the ball is now in MDCO's court with regards to a possible bidding war. With an experienced activist Board of Directors, we believe maximum shareholder value will continue at MDCO as the company has one of the most attractive de-risked drugs available for a premium takeout.

RECOMMENDATION

MDCO is a BUY under 60 with a TARGET PRICE of 85

NKTR – Five Abstracts for Bempeg and '255 at 2019 SITC

NKTR will have a strong presence at the 2019 SITC Annual Meeting being held from November 6-10, 2019, at National Harbor, Maryland (https://www.sitcancer.org/home). The presentations include an oral session with a presentation of updated data from the PIVOT-02 study of bempegaldesleukin

NKTR-255 is an IL-15 receptor agonist designed to engage the IL-15 pathway to stimulate and expand natural killer (NK) cells and promote the survival and expansion of central memory CD8+ T cells without inducing suppressive regulatory T cells. Il-15 is very similar to IL-2, the target for Bempeg in that it has a

(NKTR-214, bempeg) with nivolumab in patients with first-line metastatic melanoma.

Details of the oral presentation:

- Abstract Title: 'Clinical activity, including deepening of response, of BEMPEG plus NIVO in previously untreated patients with metastatic 1L Melanoma: results from the Phase 1/2 PIVOT-02 Study' Abstract: O35

Details of the poster presentations:

- Abstract P619: 'NKTR-255, a polymer-conjugated IL-15 receptor agonist, enhances efficacy of therapeutic monoclonal antibodies with ADCC activity in solid tumor models',
- Abstract P623: 'Bempegaldesleukin in combination with local radiation and systemic checkpoint blockade induces a robust systemic anti-tumor immunity',
- Abstract P622: 'Characterization and comparison of NKTR-255, a polymer-conjugated IL-15 versus IL-15 superagonist'

Details of the Trials in Progress poster presentation:

- Abstract P387: 'A Multicenter, Open-Label, Exploratory Platform Study to Evaluate Biomarkers and Immunotherapy Combinations for the Treatment of Patients with Metastatic Castration-resistant Prostate Cancer (PORTER)'

very short half-life in the body limiting its therapeutic effectiveness. NKTR's unique polymer technology allows '255 to slowly and effectively deliver IL-15 at therapeutic levels without the toxicity associated with using large amounts of naked IL-15.

The data at SITC has the potential to serve as a catalyst for NKTR's stock, particularly from its current depressed levels, as the Street has almost completely discounted the Company's oncology program. For bempeg, we expect additionally clarity regarding the data and differentiation between the two "bad" lots of drug and the properly manufactured bempeg. '255 is a very interesting I/O molecule and is underappreciated as it sits in the negative shadow of bempeg's declining data. In our view, the bempeg data will begin to demonstrate the difference between good and bad manufactured lots which should also help heal confidence in management and appreciate the potential of both '214 and '255. Given the recent stock weakness we are lowering our BUY to 35 (from 70) and our TARGET to 60 (from 100). NKTR still has over $1.8 billion in cash on hand, a growing revenue stream, a real pipeline and with a $3.1 billion market cap we believe the stock is oversold and undervalued.

RECOMMENDATION

NKTR is a BUY under 35 with a TARGET PRICE of 60

SGMO – New CMO; Busy Event Calendar Ahead – BUY

Despite the depressing stock price (along with the majority of the XBI), Sangamo continues to make

We believe the start of the fourth quarter will begin a period of important clinical activity for SGMO, with a

meaningful progress and has a busy catalyst calendar remaining in 2019 and beyond. This week, the Company announced that is has hired a new Chief Medical Officer, Bettina Cockroft, who fills previous CMO Ed Connor's slot (Connor left back in May). Cockroft brings 23 years of global experience in biotech (CYTK, AURS and Merck-Sorono, etc.) with a focus on neurological disorders that, among other programs, bodes well for SGMO's proprietary CNS gene regulation platform (e.g., tauopathies).

Busy Event Calendar About To Start

In addition to presenting at the Gene and Cell Therapy at the Mesa and several investor conferences this past week and in the week ahead, the Company has one of the busier clinical trial calendars approaching:

- October 2-4 – Cell & Gene Meeting on the Mesa (https://www.meetingonthemesa.com)
- October 4 – Cantor Global Healthcare Conference
- October 7 – Chardan 3rd Annual Genetic Medicines Conference
- October 8 – Jeffries Gene Editing/Therapies Summit
- ~ November 14 – Q3:19 Quarterly earnings release/conference call
- December 7-10 – ASH (https://www.hematology.org/Annual-Meeting/) – SB-525 – hemophilia A Phase II update; initiation of Phase III (YE:19)
- Q4:19 – ST-400 – Additional preliminary data in beta-thalassemia/sickle cell disease (https://www.thalesclinicalstudy.com) by SGMO/BIIV/SNY
- YE:19 – SB-920 STAAR study update of first patient in Fabry's disease (https://clinicaltrials.gov/ct2/show/NCT04046224?term=Sangamo+Fabry%27s&rank=1)
- Y/E – TX-200 – initiate Phase I/II trial in solid organ transplant (RCC)

key focus on SB-525 gene therapy for hemophilia A. The market has all but written off hem A gene therapies recently with first mover BMRN's most recent data being underwhelming. While this may have dimmed the outlook for BMRN, it opens the door for SGMO's update (most likely at ASH) where we strongly believe that several competitive advantages will emerge (e.g., efficacy, durability and safety). In our view, SB-525 will begin to gain investor attention as ASH approaches.

RECOMMENDATION

SGMO is a BUY under 20 with a TARGET PRICE of 30

ZIOP – (9/26/19) – Sleeping Beauty TCR Solid Tumor Trial Posted By NIH Starts Next Week, Oct. 1, REITERATE BUY

The trial discussed below is the accumulation of decades of work by the world's leading cancer gurus. While CAR-Ts have shown remarkable successes in blood cancers, treating solid tumors with CAR-Ts has proven to be quite challenging. The ZIOP/NIH partnership has both the T-cell expertise and technology required to treat solid tumors with TCRs utilizing the proprietary *Sleeping Beauty* non-viral gene transfer system. The ability to treat solid tumors with TCRs has game changing potential.

Under Dr. Steven Rosenberg, the NIH has posted the following Phase II clinical trial using Ziopharm's Sleeping Beauty system (https://clinicaltrials.gov/ct2/show/study/NCT04102436?term=Sleeping+Beauty&rank=1&show_desc=Y#desc):

Objective – To determine the rate of objective response (using RECIST v1.1 criteria) of patients with solid cancers who receive autologous PBL that have been genetically modified with genes encoding TCRs that recognize mutated neoantigens in the autologous cancer using the Sleeping Beauty system. This is the beginning of the clinical program using ZIOP's TCR technology, sponsored by the NIH and Dr. Rosenberg's lab. The breadth of the applications are notable by the four major tumor types included. REITERATE BUY

A enrollment total of 210 patients is expected who have measurable solid cancer with at least one lesion that is resectable for TIL generation with minimal morbidity plus at least one other lesion that can be measured that falls into one of four cohorts: (1) gastrointestinal and genitourinary, (2) breast and

Condition or Disease	Intervention/treatment	Phase
Glioblastoma Non-Small Cell Lung Cancer Breast Cancer Gastrointestinal/Genitourinary Cancer	Drug: Fludarabine Drug: Cyclophosphamide Drug: Aldesleukin Biological: **Sleeping Beauty** Transposed PBL	Phase 2

All patients will receive a non-myeloablative lymphodepleting preparative regimen of cyclophosphamide and fludarabine. Patients will then receive the infusion of autologous transposed PBL and begin high-dose aldesleukin (720,000 IU/kg IV every 8 hours for up to 10 doses). Clinical and immunologic response will be evaluated approximately 4-6 weeks after cell infusion and periodically thereafter.

It is anticipated that approximately one patient per month will enroll into the trial for each of the four histologic groups. Thus, accrual of up to 4 x 50=200 total evaluable patients may be completed in approximately 2-4 years. Importantly, these four tumor types make up the most common solid tumors.

The NCI team has used the Sleeping Beauty platform to generate neoantigen-specific T cells and is looking forward to initiating a clinical trial infusing these genetically modified T cells to target solid tumors. The Sleeping Beauty system is able to target multiple unique mutations that give rise to a patient's malignancy. Potential antigens expected to be incorporated include EGFR, p53 and KRAS, amongst many others as they are discovered.

Why Sleeping Beauty?

Sleeping Beauty's non-viral gene transfer system is well suited for developing genetically modified TCR therapies that target multiple neoantigens because of

ovarian, (3) non-small cell lung cancer (NSCLC), and (4) glioblastoma. Metastatic disease is required for Cohorts 1-3 but not for Cohort 4.

Design

Patients will undergo resection or biopsy to obtain tumor for generation of autologous TIL cultures. Patients will be entered into four cohorts that include (1) gastrointestinal and genitourinary tract cancers, (2) breast and ovarian cancers, (3) non-small cell lung cancer (NSCLC), and (4) glioblastomas. Exome sequencing and often RNA Seq will be performed to identify the mutations expressed in the patient's cancer. Multiple autologous TIL cultures will be grown and tested for reactivity against mutations from the autologous tumor using assays we have developed that involve the exposure of autologous antigen presenting cells to long peptides containing the mutation or tandem mini genes encoding the mutation.

T-cell cultures with reactivity against mutations will be identified and the individual TCRs that recognize the mutation will be synthesized and used to transfect the TCR into the patient s autologous PBL using the Sleeping Beauty system.

Transposed autologous PBL will then be expanded to large numbers using our standard rapid expansion protocol and administered to the patient following a non-myeloablative lymphodepleting regimen.

its very rapid manufacturing capability. For patients receiving genetically modified TCRs targeting their own neoantigens in their cancer cells, there will be a need for a manufacturing process to make one product per patient. The manufacturing process will need to be fast, scalable and cost effective, and Sleeping Beauty checks all of these requirements. This trial will begin enrolling next week, Oct.1, and the press release should draw attention to ZIOP and the vast potential to treat solid tumors with TCRs. It is possible that we may see the first data late in 2019 as patients will be evaluated after just 4-6 weeks of treatment.

RECOMMENDATION

ZIOP is a BUY under 5 with a TARGET PRICE of 12

ZIOP – Receives FDA IND Clearance for 3rd Generation CAR-T, Key Clinical Catalysts Nearing – BUY

ZIOP recently announced that the FDA has cleared an investigational new drug application (IND) for a Phase I trial to test their 3rd generation CD19-specific CAR-T,

The initiation of this Sleeping Beauty study is rather important for ZIOP and immuno-oncology as a whole. First, ZIOP's 3rd gen CAR-T has the potential to

produced using a process termed rapid personalized manufacture (RPM), as an investigational treatment for patients with relapsed CD19+ leukemias and lymphomas. These are very sick patients who have no treatment options left as they have relapsed in the months following allogeneic bone marrow transplant (aBMT), with some having a median survival of only 2-3 months.

The IND clearance builds upon ZIOP's experience with two prior generations of immunotherapy trials using the *Sleeping Beauty* platform, which it believes is the ***most clinically-advanced non-viral approach to the genetic modification of T cells.*** With this third-generation trial, DNA from the Sleeping Beauty system is stably inserted into the genome of resting T cells to co-express a chimeric antigen receptor (CAR), membrane-bound IL-15 (mbIL15) and a safety switch, which is designed to reduce cost, simplify production, and preserve the therapeutic potential of the T cells.

Up to 24 patients will be enrolled in the study to evaluate the infusion of donor-derived RPM CAR-T in patients with CD19+ leukemias and lymphomas who have relapsed after allogeneic BMT. This study will be conducted at The University of Texas' MD Anderson Cancer Center, one of the world's premier oncology research hospitals, under an investigator-initiated trial expected to begin later this year.

significantly enhance efficacy in very late-stage cancers. Next, it will greatly reduce the high costs relative to first generation CAR-Ts (currently in the ~$500,000 per patient) range. Finally, the IND sign-off by the FDA also validates ZIOP's manufacturing system as safe. This is very critical as the agency has repeatedly emphasized the importance of having safe manufacturing processes when it comes to cell and gene therapies. *ZIOP's technology promise is beginning to become reality. More novel trials are due to start soon (e.g., Rosenberg's lab).*

RECOMMENDATION

ZIOP is a BUY under 5 with a TARGET PRICE of 12

The Back Page

Symbol	Company	Orig.Rec.	Current	Target	Recommendation
ACAD	Acadia	33.79	38.30	60	BUY under $46
ALKS	Alkermes	10.13	18.84	75	BUY under $55
BMRN	BioMarin	12.68	64.82	130	BUY under $100

ESPR	Esperion	24.42	37.49	100	BUY under $75
FPRX*	Five Prime*	16.29	3.64	16*	BUY under $8*
INCY	Incyte	5.88	74.88	95	BUY under $75
XON	Intrexon	34.42	5.92	24	BUY under $12
IONS	Ionis	7.63	58.56	90	BUY under $75
MDGL	Madrigal	17.00	85.97	275	BUY under $200
MDCO	Medicines Company	31.98	50.03	85	BUY under $60
MYOV	Myovant	13.74	5.00	25	BUY under $17
NKTR*	Nektar*	4.66	18.20	60*	BUY under $35*
PCRX	Pacira	15.78	38.39	55	BUY under $40
SGMO	Sangamo	4.77	8.62	30	BUY under $20
ZIOP	Ziopharm	8.00	4.25	12	BUY under $5
ZYNE	Zynerba	8.00	7.86	27	BUY under $18
CRSP	Crispr	58.39	38.79	40	HOLD
EDIT	Editas	36.13	21.64	26	HOLD
NTLA	Intellia	31.63	11.96	21	HOLD

**new recommendation*

THE MODEL PORTFOLIO*

COMPANY	SHARES OWNED	TOTAL COST	TODAY'S VALUE
Long Positions			
Acadia	5,000	156,557	191,500
Alkermes	4.000	88,690	75,360
Esperion	3,491	105,316	130,878
Five Prime	7,250	91,136	26,390
Incyte	1,294	34,817	96,895
Intrexon	10,200	76,510	60,384
Ionis	3,250	49,123	190,320
Madrigal	3,292	69,980	283,013
Medicines Co	4,600	77,400	230,138
Myovant	7,500	103,853	37,500
Nektar	6,500	63,277	118,300
Pacira	2,500	63,887	95,975
Sangamo	20,479	253,596	176,529
Ziopharm	27,500	166,100	116,875
Zynerba	27,500	150,003	84,338
(10/4/19)		**Equities:**	**$1,914,394**
		Cash:	**$31,953**

PORTFOLIO	**VALUE:**	**$1,946,347**

**The Model Portfolio is designed to reflect specific recommendations. We began the Model Portfolio on 12/23/83 with $100,000. On 4/13/84, we became fully invested. All profits are reinvested. Stocks recommended since then may be equally attractive, but may not be in the Model Portfolio. Transactions and positions are valued at closing prices. No dividends are created, and we don't use margin. Interest income is credited only on large cash balances.*

THE TRADER'S PORTFOLIO**

COMPANY	SHARES OWNED	TOTAL COST	TODAY'S VALUE
Long Positions			
Acadia	5,000	156,557	191,500
Alkermes	3,500	83,184	65,940
Esperion	4,075	100,005	152,772
Five Prime	8,020	124,919	29,193
Incyte	2,229	51,176	166,908
Intrexon	10,170	119,952	60,206
Ionis	3,300	53,501	193,248
Madrigal	2,910	49,964	250,173
Medicines Co	4,250	127,405	212,628

Myovant	7,410	102,831	37,050
Nektar	6,000	36,411	109,200
Pacira	2,000	55,918	76,780
Sangamo	20,479	253,596	176,529
Ziopharm	27,500	166,100	116,875
Zynerba	27,500	166,100	56,223
(10/4/19)		**Position Total:**	**$1,895,223**
		Margin:	**–$1,249,937**
	PORTFOLIO	**VALUE:**	**$645,286**

***The Trader's Portfolio joined the Model Portfolio on 1/6/05 with $500,000 and is designed to take advantage of short-term opportunities throughout the biotech sector. The Trader's Portfolio will hold both long and short positions in stocks, trade-in options, and use margin. These strategies increase risk. Although there is no limit on the time any purchase can be held, the time frame for most investments will be weeks to months.*

BENCHMARKS

	NASDAQ	S&P 500	MODEL	TRADER'S
Last 2 Weeks	-3.7%	-3.2%	-7.8%	-20.0%
2019 YTD	18.6%	16.1%	-10.7%	-18.9%
Calendar Year 2018	5.7%	6.6%	4.5%	11.2%

Calendar Year 2017	29.3%	19.9%	65.6%	98.9%
Calendar Year 2016	7.5%	9.5%	-29.6%	-30.5%
Calendar Year 2015	-0.1%	-0.1%	25.1%	27.9%
Calendar Year 2014	13.4%	11.4%	29.2%	45.0%
Calendar Year 2013	38.3%	29.6%	103.4%	214.7%
Calendar Year 2012	13.4%	15.9%	25.7%	68.7%

New Money Buys

NEW MONEY BUYS

(Based on Market Cap when under our limit)

1st Tier: ALKS, BMRN, INCY, IONS, NKTR

2nd Tier: ACAD, ESPR, MDGL, MDCO, MYOV, PCRX, XON, SGMO

3rd Tier: FPRX, ZIOP, ZYNE

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