Prohost BioTechnology
Biotechnology Research and Investment
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Stories, Statements and Observations

On December 8, 2016 under News & Comments Prohost commented on President Elect Trump's statement that he is going to bring down the exorbitant drug prices.

The Skyrocketing Prices of Drugs

Like everybody else we happen to talk to, we agree that the prices of drugs have skyrocketed to a level that made them unaffordable. It is a serious problem that requires a prompt serious action – an investigation that can detect the root-causes of the problem, unearth them and sever them once and for all.

What we did not agree with, though, is jumping into conclusion, prior to any investigation that the exorbitant prices of drugs emanate solely from the pharmaceutical industry. We do not agree that the biotech firms and pharmaceutical firms should be devastated when other firms that are supposed to negotiate the drug prices with the drug firms on behalf of the pharmacies and the consumer do their job instead on their own behalf. When they reach the agreement and obtain their lower prices, they raise the prices and put the difference in their large pockets. These firms contribute nothing to the healthcare system. They do not contribute to research, development of drugs, clinical trials or marketing. All they do is suck the blood of the healthcare budget.

Those same parasites keep blaming the drug firms and do whatever it takes to devastate them, opening the door to more corruption, in addition to freezing the unprecedented evolution of life sciences.

Trump's statement caused a selloff in the biopharmaceutical stocks in spite of the fact that Mr. Trump has not mentioned what he will do to lower the drug prices. He did not pinpoint the drug companies as the culprits. Most probably, the president Elect would conduct an investigation before making accusations. We see no interest anywhere to anybody in bringing down medical research, which is conducted by the biotech and pharmaceutical firms, or in paralyzing the advancement made in the life sciences by devastating the source of the energy made possible the evolution of clinical sciences.

"The President Elect did not mention
the drug companies. All he said is that he is going
to bring down the drug prices,
which, is what Everybody Wants."

The only way to lower the drug prices is to start by appointing neutral experts in a committee whose job would be to pinpoint the entities that feed on the healthcare budget without contributing anything positive or valuable to healthcare. A job well done towards lowering the price of drugs would be correctly diagnose the problem and then look for a solution.

Gilead: What the Firm's President Said and What he Omitted to Say

In an article written by Alex Keown -- BioSpace.com Breaking News Staff We Read, "Speaking to a healthcare summit hosted by Forbes, Gilead President Milligan said the company priced Sovaldi, which has a near-cure rate of about 98 percent, at the same price as the existing treatments that had an efficacy rate of about 50 percent. That price point was something that Gilead thought was a good value. He said the company did not have a "good enough conversation" with the payers and that Gilead was conservative in what it said to the payers, which did not prepare them for the number of patients who came forward for the HCV treatment.

Milligan talked about a huge surge of patients. He added that hundreds of thousands of patients came forward and the tidal wave of patients created "a lot of anxiety around payers" and created an "an outcry against us for having mispriced the product. He said, we quote, "Honestly, it was far more than we thought. We did not think the system could or would try to handle as many patients as it did. We essentially quadrupled the number of patients treated in a year. That surge really created a lot of pain."

Forbes John LaMattina said Milligan was being overly apologetic and that the outcry against Gilead's pricing goes against the claims that this is the type of therapy they want the biopharmaceutical industry to produce.

The price of Sovaldi is Something of a Bargain
when Compared to the Price of other
HCV Drugs, which are Less Effective.

LaMattina added, "The price of Sovaldi is something of a bargain when compared to the price of other HCV drugs that are less effective. The high price tag of Sovaldi cannot be compared to what Turing Pharmaceuticals' price hikes of the old drug Daraprim, which saw a price spike of 5,000 percent last year when it was acquired by Turing." He also mentioned the price-inflated inflated of the life-saving EpiPen Auto-Injector.

"If a company is not going to get very good pricing for excellent new drugs, then the biopharmaceutical industry will likely stagnate and many new opportunities for drug R&D will not be able to be funded," LaMattina said. He added, "This was a great opportunity for Gilead's CEO to voice these issues. It's too bad he didn't."

Hepatitis C affects about 3.2 million Americans. Gilead's Sovaldi and Harvoni drugs are eradicating the disease. HCV infection causes many symptoms that require treatments before it causes liver cirrhosis, which would require years of futile treatments and hospitalization. The Cirrhosis ends up becoming liver failure, which requires liver transplant, or moves to becoming liver cancer. Liver transplant is expensive, can fail and can be repeated. It requires permanent use of antirejection drugs and other drugs. Transplanted liver becomes sometimes contaminated with the virus, which had to be removed. Hospitalization is frequent and surgeries might be also required. Do people know how much is the cost of managing all of the above?

Millions of dollars were to spend while the patients are being tortured. Gilead's HCV oral drugs erase the virus in 12 weeks. Can somebody thank Gilead instead of throwing stones on it? If you remember that GILD has given life to condemned AIDS patients, then double your thanks.

Learning More About

AGENUS

Since its inception, **Agenus (AGEN)**, previously known as Antigenics, trading with the same symbol was focused on immune system boosters, including vaccines and adjuvants. The firm is one of a few firms that thought about designing and worked on developing **therapeutic vaccines** at a time when all the vaccines were preventive from infective organisms, including microbial and viral. As a matter of fact, the firm has a therapeutic vaccine approved in Russia.

Immunotherapy for Cancer

Around the year 2011, the trend in oncology started to move from the use of chemotherapy radiation and surgery only to immunotherapy. Opening the door for immunotherapy in cancer was a biotechnology company called Medarex based in Princeton, N.J., which designed and developed a monoclonal antibody, ipilimumab, that targets the immune check protein CTLA-4, for metastatic melanoma. The FDA approved the drug in 2011 by the trade name YERVOY, which was the first immunotherapy not to be a vaccine, which enables the immune system cells to locate, infiltrate and attack cancer cells and wipe them off.

Two years Before YERVOY was granted FDA approval in 2011, Medarex was acquired by Bristol-Myers Squibb. Three years later, in 2014, the FDA granted approved Opdivo (nivolumab), a monoclonal antibody targeting another checkpoint protein PD-1 for advanced melanoma. On year latter, in 2015, the FDA expanded YERVOY approval to also treat squamous non-small-cell lung carcinoma.

Now, there are three marketed checkpoint antagonists for cancers. They are:

Yervoy (ipilimumab) and **Opdivo (nivolumab)** for Bristol-Myers Squibb; **Pembrolizumab (Keytruda)** for Merck and **Atezolizumab (Tecentriq)** for Genentech Oncology

What all the above has to do with Agenus?

Without knowing about the checkpoint inhibitors we will never understand Agenus' near-term and long-term plans and strategies. We will never know the meaning and importance of the pipeline of checkpoint proteins to be targeted for inhibition, which fill the firm's pipeline.

Immunotherapy products, especially checkpoint inhibitors have demonstrated better, if not superior results in combination treatments. Therapeutic combinations require the drugs to be synergetic, i.e., can be effectively used together, which led Antigenics to conduct studies that demonstrate its checkpoint inhibitors are indeed synergetic and can be used together according to the firm's reports.

Only three Checkpoint proteins are targeted by the 4 marketed checkpoint antagonists. The fact is that there are many other checkpoint proteins that can be used by cancer to put a break on the immune system T cells, preventing them from attacking cancer cells. This reality would explain the importance of the value of the checkpoint targets for inhibition that fill Agenus' pipeline, which attract pharmaceutical firms such as Merck to partner with Agenus.

The reason why Antigenics develop a drug that targets for inhibition **CTLA-4** checkpoint, in addition to PD-1 is that inhibiting CTLA-4 activates the immune system and enables it to reach and attack cancer cells and the checkpoint inhibition makes the activation durable.

It is obvious that **CTLA-4 and PD-1 antibody** and other **checkpoint antagonists** are the focal point of Agenus cancer immunotherapy or immune-oncology strategy. They are the essential part of the firm's immune-oncology pipeline.

Agenus anticipates more future corporate collaborators to combine the firm's pipelines of checkpoints, and of antibodies with its foundational checkpoint antagonist, **AGEN1884** and **AGEN2034**, in addition to its vaccine platforms **Prophage, AutoSynVax** and other vaccines targeting phosphorylated peptide. Agenus believes that combining these modalities based on necessity is integral to its success, which is the base of the firm's strategy.

Agenus Immune-Oncology Programs

AGEN1884: This product is an antibody antagonist for **CTLA-4.** It entered Phase 1 trial in April this year and is the **only clinical stage antibody therapeutic for this target besides Bristol-Myers (BMS) approved blockbuster drug Yervoy and AztraZeneca's drug Tremelimumab**.

AGEN2034: Is one of Agenus **PD-1 antagonists**. This drug is expected to move into clinical trial in the first quarter of 2017.

What Agenus intends to do most in 2017 will be to **initiate combination studies with CTLA-4 and PD-1 in checkpoint antagonist** for designated indications.

*Agenus immunotherapy drugs are **checkpoint inhibitors**. The checkpoint proteins put a break on the immune system's cells, preventing them from attacking the normal healthy body cell causing autoimmune inflammatory diseases. Unfortunately, cancers seem to be faster than human researchers in sensing the presence of these checkpoint proteins and understanding their ability to limit the T-cell actions including attacking them. As a matter of fact, cancers played the agonist role, which accentuated the effect of checkpoints on the immune system cells in order to stop these cells from attacking them. When scientists learned about these checkpoints and their action, they developed drugs that antagonize their actions so that the immune system's cells can restore its capability to find and attack cancer cells and kill them.*

Good news is that Agenus checkpoint inhibitors antibodies **AGEN1884** targeting **CTLA-4 checkpoint** and **AGEN2034** targeting **PD-1 checkpoint** have distinct **synergistic** modes of action, meaning that can benefit each other not the contrary.

Blocking CTLA-4 leads to recruiting and activating the T-cells into the tumors. PD-1 inhibition prevents the suppression of activated T-cells, hence, expands the representation of T-cell clones that recognize the tumor and enhance its destruction.

Also, CTLA-4 blockade helps **activates CD4 cells**, contributing to a more stable immune response.

CTLA-4 antagonist may also be synergistic for combinations **with the new generation of novel checkpoint antibodies, a number of which are present in Agenus portfolio.**

Again, we observe that CTLA-4 blockade functions in part upstream of PD-1 and **enhances activation and recruitment of T-cells into tumors**. PD-1 inhibition prevents the suppression

of activated T-cells and deepens the representation of individual T-cell clones that recognize the tumor, enhancing tumor destruction. In addition, there is now emerging evidence that CTLA-4 blockade facilitates activation of CD4 cells, thus potentially contributing to long-term memory formation and a more stable immune response.

Bottom line, Agenus is making progression in the checkpoint modulator antibody programs, including those targeting CTLA-4, PD-1 and others.

Merck has partnership on undisclosed targets

Agenus CTLA-4 antagonist is one of only three such therapeutics in the clinic. The two other clinical CTLA-4 molecules are the product Yervoy that they have developed at BMS and the second is still in clinical development with AstraZeneca.

AGEN anti-CTLA-4 monoclonal antibody has been in the clinic since April of this year and Agenus reported it is on track to complete the characterization of its safety profile by Q1 of 2017.

Near-Term Possibilities and Priorities

Two of Agenus molecules are currently in Phase 1 and another three antibody programs poised to reach first in man studies within the next six months. **We anticipate some results.**

Agenus priorities are focused on the development of its clinical programs that would generate quick clinical data, which would provide a clear path towards drug development, combinations and registration and commercialization.

Entering into new partnerships, which would replenish the firm's cash position, reduce the cash burn rate, thus, opens the door to an uncomplicated execution of ambitious strategy.

filing a combination of **AGEN1884 with a commercially available PD-1 antagonist in first line solid tumors** in which anti-CTLA-4 and PD-1 antagonists have proven activity.

Validating the strategy and subsequently the clinical activity of AGEN1884 when combined with an established PD-1 antagonist. A successful outcome would make Agenus the first to do this key milestone for an anti-CTLA-4.

PD-1 antagonist, AGEN2034 entering the clinic in early 2017.

Initiating combination studies of **AGEN2034** and **AGEN1884** for second-line tumor as soon as the pharmacodynamics, pharmacokinetic and safety profile of AGEN2034 will be established. This is anticipated to occur in the **second half of 2017.**

FDA decision on the shingles vaccine in partnership with GlaxoSmithKline. GSK has filed a biologics license application to the FDA for the prevention of shingles. The vaccine includes an adjuvant system that contains QS-21 Stimulon, which is Agenus' proprietary adjuvant, which it has not exclusively licensed to GSK. The submission to the FDA was preceded by articles published in the May and September issues of the New England Journal of Medicine, reporting on the tremendous efficacy of the vaccine in patients aged 50 years and older and 70 years and older. The remarkable protection that this vaccine confers against shingles, even in the elderly, highlights the benefits of Agenus' powerful **adjuvant QS-21 Stimulon**. This has allowed for

remarkable clinical results to be achieved with a sub unit vaccine that doesn't require the use of a live attenuated virus, thus greatly improving the safety of this vaccine.

To Be Continued in Part 2
To Be Posted Tomorrow After Market Hours

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