Companies wager high on CD38-targeting drugs for blood cancer

On 30 August, the Danish biotech GenMab signed a $1.1 billion deal turning over licensing rights for its experimental blood cancer drug daratumumab to Janssen, a Pennsylvania–based subsidiary of Johnson & Johnson. The high price tag for the deal signals the faith that drug developers have in an emerging class of medicines designed to treat blood cancers in a targeted fashion. These drugs, which include daratumumab, work by aiming at a specific protein called CD38. The protein is found on the surface of many immune cells, including plasma B cells, which become malignant in cancers such as multiple myeloma—and many hope that targeting CD38 will spare healthy cells that lack this marker.

Daratumumab has many hurdles to overcome before reaching the market, but the human monoclonal antibody therapy has shown promise in an early trial presented in June at the annual meeting of the American Society of Clinical Oncology in Chicago. The phase 1 safety study conducted in Denmark in 29 patients with multiple myeloma found evidence that the drug had killed at least some portion of malignant plasma B cells in all of the participants. There are now more phase 1 and 2 safety and efficacy trials of daratumumab ongoing in patients with this type of cancer. "The early results we've seen have been quite surprisingly and happily good," says Nikhil Munshi, an oncologist at Dana Farber Cancer Institute in Boston who was not involved in the trial.

Hot on the tail of daratumumab, at least two human antibodies targeting the CD38 protein are in preclinical development for use against multiple myeloma: France's Sanofi has a drug known as SAR650984 in the works, whereas MorphoSys in Germany is working on one known as MOR03087. These antibodies, like daratumumab, recognize CD38 on the surface of cells and mark them for destruction, either by healthy, functioning immune cells or via programmed cell death.

Current treatments for blood cancers rely on disrupting the tumor environment by restricting blood flow to tumors in lymph nodes and bone marrow, where plasma cells originate, and by killing tumor support cells in the bone marrow. The CD38-targeted antibody approach "can be a game changer in myeloma because it represents a totally new mode of action that will not compete, but complement available therapies," says biotech analyst Ohad Hammer of the Israeli venture capital firm Pontifax, who has studied the rise of CD38-targeted drugs. If the new drugs are, as they appear, more effective and less toxic than the current standard treatments for multiple myeloma, Hammer says the market potential could be significant. "Antibodies like this are the fastest growing and most promising segment of the biotech industry," he says.

But, while patients with multiple myeloma stand to benefit soonest from CD38-targeted drugs if they make it to the market, scientists have high hopes for such drugs to be used in an even wider range of blood cancers. GenMab chief executive Jan van de Winkel told reporters and investors at a 30 August press conference that his company's drug could potentially treat "a number of other cancer indications" such as acute myeloid leukemia, acute lymphoblastic leukemia and follicular lymphoma.

The cancers van de Winkel lists all involve malignant B cell progenitors, immune system warriors that have gone rogue on their way to becoming B cells. But even though scientists say that drugs such as daratumumab could potentially help patients with this wide array of cancers, they stress that the effectiveness to treat a given cancer type will depend on the proportion of malignant immune cells that express high amounts of CD38. The more strongly the cancer cells express the protein, the more easily these drugs can find and thwart them. Still, researchers say that despite the many unknowns, the field is eager to see how CD38 drugs perform. "This is new, but it is beginning to create buzz," says Munshi. "It is very exciting where these therapies are going."

Rebecca Hersher

Despite quintuple disappointments, Lilly still charms investors

Analysts took note in September when, in the span of a month, Eli Lilly delivered negative results from five phase 3 trials on agents ranging from blood thinners to cancer therapy. The disappointments underscored the difficulties faced by the Indianapolis-based drug maker, which lost patent protection on its best-selling bipolar drug Zyprexa (olanzapine) last year and will lose US market exclusivity in December on its popular antidepressant Cymbalta (duloxetine).

Despite the turmoil, investors still seemed unfazed as of mid-September, when Lilly's stock prices stood $10 higher than in the same period last year. The poor trial outcomes of the company did not put off the market because "the failures they have had did not come with high expectations [from investors] to begin with," explains Tim Anderson, an analyst with the wealth management group Sanford C. Bernstein & Co. in New York. In part, Lilly gave itself a boost when it mined existing data from two failed trials of the Alzheimer's disease drug solanezumab and found that the drug possibly slowed progression in mild to moderate presentations of the disease. "The fact that there is some positivity there is more than what was expected," says Anderson. Here's a look at the hiccups investors looked past:

7 Aug – Post-menopausal women suffering from back pain due to osteoporotic vertebral fractures fared no better when they were treated with a teriparatide injection, called **Forteo**, in a 710-person comparative study than when they received Actonel (risedronate).

24 Aug – Initial results from two 1,000-person studies of patients with Alzheimer's disease receiving **solanezumab** did not meet either study's cognitive or functional endpoints. However, when Lilly combined data from the two trials and excluded severe cases, it found potentially positive effects in participants with mild to moderate symptoms of the disease.

26 Aug – In a comparative study involving 10,300 participants, Lilly's blood-thinner drug **Effient** (prasugrel) did no better in preventing heart attacks, strokes or other forms of cardiovascular death than clopidogrel.

29 Aug – The company halted a trial of the late-stage schizophrenia drug **pomaglumetad methionil** when an independent analysis of data showed the trial would probably not meet end points outlined for the 1,100 enrolled participants.

6 Sept – A combination treatment for nonsquamous non–small-cell lung cancer that included an injection of **Alimta** (pemetrexed) failed to improved overall survival of patients in a 900-person study.

Kathleen Raven