CCR5-Blocking Antibody Leads to Long-Term HIV Suppression

Leronlimab (PRO 140) also shows promise as a treatment for cancer and graft-versus-host disease.

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A monoclonal antibody targeting the CCR5 receptor on T cells maintained HIV suppression in people who switched from oral combination antiretroviral therapy in a mid-stage study, paving the way for a larger Phase III clinical trial, according to a press release issued by CytoDyn.

The company also announced this week that the Food and Drug Administration (FDA) has granted fast-track status for leronlimab, formerly known as PRO 140, as a treatment for hard-to-treat triple-negative breast cancer that expresses CCR5.

Leronlimab for HIV

HIV uses the CD4 receptor on T cells plus a second coreceptor—either CCR5 or CXCR4—to enter cells. An estimated 70% of people with HIV and up to 90% of those with a recent diagnosis have virus that uses CCR5. The oral entry inhibitor Selzentry (maraviroc) also works by blocking CCR5. There is currently only one monoclonal antibody used to treat HIV, the recently approved CD4 blocker Trogarzo (ibalizumab).

For several years now, CytoDyn has been presenting results from studies of leronlimab at scientific conferences—and in numerous press releases—as it makes its way through the clinical trials process.

After an early study showed that a single IV infusion of leronlimab had potent antiviral activity, scientists developed a new formulation that could be given by subcutaneous injection once weekly, allowing for self-administration.

A Phase IIb study evaluated leronlimab as weekly maintenance therapy for people who had achieved viral suppression using a standard oral combination antiretroviral regimen. They stopped their current antiretrovirals a week after starting leronlimab.

In 2016, researchers reported that leronlimab maintenance monotherapy kept viral load undetectable for more than a year in about a third of people with CCR5-using virus. Follow-up continued, and updated findings the following year showed that among those with viral

suppression who stayed on leronlimab, 63% still had undetectable virus at two years.

CytoDyn announced this week that it now has enough data to more precisely design a pivotal Phase III trial to support a maintenance monotherapy indication for leronlimab. Researchers have confirmed that the half-life of the antibody is longer than previously believed—10 days rather than three days. In order to reduce the risk of viral rebound when switching from oral antiretrovirals to leronlimab, the new protocol calls for the antibody to overlap with the existing regimen for a month instead of a week.

However, the real unmet need in HIV treatment is for people who have developed resistance to most or all available antiretrovirals and have few remaining treatment options.

Another study evaluated leronlimab in people who had a detectable viral load during the three months prior to enrollment and resistance to at least two antiretroviral drug classes. In the first part of this Phase IIb/III trial, 52 participants were randomly assigned to receive a single injection of leronlimab or a placebo in addition to their current failing regimen.

As reported at last year's ASM Microbe conference, after a week, 64% of people in the leronlimab group saw their viral load fall by at least a half a log—considered a clinically meaningful drop—compared with about a quarter of those in the placebo group. CD4 counts rose by about 80 cells on average.

Participants then began receiving weekly injections of leronlimab on an open-label basis along with an optimized background regimen, meaning resistance testing was used to select the antiretrovirals most likely to be active against each individual's virus. This study is ongoing.

In both the maintenance monotherapy and combination therapy studies, leronlimab was generally well tolerated. The most common side effect was mild or moderate injection-site reactions. Participants have not shown a change in HIV tropism that would allow their virus to use the CXCR4 coreceptor instead of CCR5; to date, the antibody does not appear to negatively affect normal immune function by blocking CCR5.

The FDA has granted fast-track status for leronlimab as part of a combination regimen for people with drug-resistant HIV, and CytoDyn has said it expects an approval decision by late 2019 or early 2020.

Leronlimab for Breast Cancer

Leronlimab also shows potential as a treatment for cancer. The CCR5 receptor appears to play a role in tumor invasion and metastasis, and laboratory and animal studies have shown that drugs that block CCR5 can stop metastasis of breast and prostate cancer, according to CytoDyn.

In addition, CCR5 regulates immune cell migration to sites of inflammation. CCR5 on donor stem cells appears to promote the development of graft-versus-host disease, and blocking the receptor may help control this life-threatening complication of bone marrow transplants for cancer

treatment.

CytoDyn is currently conducting a Phase II study to evaluate leronlimab for the prevention of graft-versus-host disease, and it is now starting a clinical trial of leronlimab plus carboplatin chemotherapy for CCR5-positive metastatic triple-negative breast cancer.

Breast cancer is classified by the type of receptors it expresses. A majority of breast cancers have receptors for estrogen or progesterone, and treatment usually includes hormone therapy. Around 20% of breast tumors express HER2 and can be treated with targeted therapies like Herceptin (trastuzumab). Triple-negative breast cancer doesn't carry any of these receptors and is therefore harder to treat. But some of these tumors do express CCR5, making them susceptible to CCR5-blocking therapies like leronlimab.

Clinical trial sites for the breast cancer trial include Quest Clinical Research in San Francisco, Northwestern University Medical School in Chicago, Houston Methodist Hospital, Vanderbilt University in Nashville and Sidney Kimmel Cancer Center in New York City.

This indication received the FDA's fast-track designation, which aims to speed up the development and review of drugs for serious conditions that fill an unmet medical need.

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