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DEAL WATCH

Merck invests in pioneering cytomegalovirus programme

Merck has agreed to pay AiCuris US$142 million upfront and up to an additional $429 million in milestone payments for its human cytomegalovirus (CMV) programme, including its lead compound letermovir, an oral CMV terminase complex inhibitor that has successfully completed Phase II trials.

CMV is a common herpesvirus that can infect people of all ages, remaining latent within the body but reactivating and shedding when the immune system is compromised. Although most people infected with CMV typically exhibit few or no symptoms, severe and life-threatening infections — characterized by fever, pancytopaenia and inflammatory changes in multiple organs — often occur in immune-incompetent or immunodeficient individuals, such as transplant recipients, HIV/AIDS patients and newborn babies.

A small number of antiviral drugs (all of which inhibit the viral DNA polymerase) are available for the treatment of CMV but their use is restricted by dose-limiting toxicity and drug resistance. "The key treatment options for CMV are intravenous ganciclovir and oral valganciclovir. Both work reasonably well, although bone marrow toxicity can be limiting and resistance can occur, especially if the drug is under-dosed. In stem cell transplant patients, this is particularly problematic since their bone marrow is tenuous at best. There are two other alternatives, intravenous foscarnet and cidofovir, but both have significant nephrotoxicity," explains David Snydman, Tufts University School of Medicine, Boston, Massachusetts, USA.

The development of less toxic therapeutic agents, that are capable of addressing antiviral-resistant CMV disease, is much needed. "An ideal anti-CMV agent would be potently active, have a clean safety profile and maintain therapeutic drug levels in target tissues when given orally at a well-tolerated dose and in a convenient dosing interval. This novel agent would preferably work through a mechanism of action that is not shared by available anti-CMV drugs and thus be active against CMV strains that are resistant to currently approved drugs," says Jeffery Meier, University of Iowa, USA. However, several issues have hampered the development of novel therapies, including the lack of an accurate preclinical animal model, disease variability and the need for prophylactic and pre-emptive treatments. "One major challenge is the way the FDA [US Food and Drug Administration] is handling the determination of clinical end points. In today's era one cannot let patients become symptomatic — when one detects CMV replication in the blood, one must intervene. Up until now, the FDA wanted manufacturers to prove a clinical end point reduction in disease, which is difficult to do given the current state of clinical practice," says Snydman.

Clinical trial data of the novel quinazoline letermovir are promising. In a Phase IIa trial in solid organ transplant recipients, letermovir was effective in treating CMV viraemia, including in a patient with a strain of CMV that was resistant to existing antivirals. And, most recently, a Phase IIb trial of letermovir for CMV prophylaxis in haematopoietic stem cell transplant recipients demonstrated significantly lower rates of prophylaxis failure with letermovir compared to placebo. Importantly, in all trials conducted to date, letermovir has been shown to be safe and well tolerated.

"There is good potential for letermovir, especially since it is reputed to have less or no bone marrow toxicity. That being the case, it might allow a prophylactic approach for prevention of CMV disease in stem cell transplant recipients," says Snydman. "Impressive results of Phase II studies support my watchful enthusiasm in going forward. Because letermovir is a highly selective inhibitor of the CMV terminase, which has no counterpart in mammalian cells, it provides a new approach in the treatment and prophylaxis of CMV infections, including CMV strains that are resistant to currently available drugs", adds Meier.

Letermovir has received orphan drug status in the European Union and the United States, where it has also been granted fast track designation.

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