US FDA grants breakthrough therapy designation to Daiichi Sankyo & Merck's raludotatug deruxtecan for patients with CDH6 expressing platinum-resistant ovarian, primary peritoneal, or fallopian tube cancers previously treated with bevacizumab

Raludotatug deruxtecan (R-DXd) has been granted Breakthrough Therapy Designation (BTD) by the US Food and Drug Administration (FDA) for the treatment of adult patients with platinum-resistant epithelial ovarian, primary peritoneal or fallopian tube cancers expressing CDH6 who have received prior treatment with bevacizumab.

Raludotatug deruxtecan is a specifically engineered, potential first-in-class CDH6 directed DXd antibody drug conjugate (ADC) discovered by Daiichi Sankyo and being jointly developed by Daiichi Sankyo and Merck, known as MSD outside of the United States and Canada.

The FDA BTD is designed to accelerate the development and regulatory review of potential new medicines that are intended to treat a serious condition and address a significant unmet medical need. The medicine is required to have shown encouraging preliminary clinical results that demonstrate substantial improvement on a clinically significant endpoint over currently available medicines.

The FDA granted this BTD based on data from a phase 1 trial and the ongoing REJOICE-Ovarian01 phase 2/3 trial. A subgroup analysis of the phase 1 trial was presented at the 2023 European Society for Medical Oncology meeting (#ESMO23). Subsequent subgroup analyses of the phase 1 trial were presented at the 2024 Society for Gynaecologic Oncology Annual Meeting on Women's Cancer and the 2025 European Society for Medical Oncology Gynaecological Cancers Congress. This is the first BTD for raludotatug deruxtecan and represents the second BTD since the start of the Daiichi Sankyo and Merck collaboration.

"Patients have limited treatment options once ovarian cancer becomes resistant to platinum-based chemotherapy, highlighting the urgent need for new medicines that can improve patient outcomes," said Ken Takeshita, MD, global head, R&D, Daiichi Sankyo. "The receipt of Breakthrough Therapy Designation represents an important step forward in our efforts to advance raludotatug deruxtecan as a novel medicine for patients with CDH6 expressing platinum-resistant ovarian, primary peritoneal, or fallopian tube cancers previously treated with bevacizumab."

"The FDA's Breakthrough Designation is a reflection of our commitment to advancing research for patients impacted by women's cancers," said Eliav Barr, MD, senior vice president, head of global clinical development and chief medical officer, Merck Research Laboratories. "Raludotatug deruxtecan has the potential to one day become an important option for the treatment of patients with CDH6-expressing platinum-resistant ovarian, primary peritoneal, or fallopian tube cancers previously treated with bevacizumab, and we are excited to share data from REJOICE-Ovarian01 with the scientific community at an upcoming medical meeting and to continue working closely with the FDA."

The two-part, multicenter, open-label, first-in-human phase 1 trial is evaluating the safety and efficacy of investigational raludotatug deruxtecan in adult patients with advanced ovarian cancer previously treated with platinum-based chemotherapy and a taxane. Patients with renal cell carcinoma resistant or refractory to standard of care therapy were originally included, but that component of the study was discontinued.

The primary objective of the first part of the study (dose escalation) was to assess the safety and tolerability of increasing doses of raludotatug deruxtecan to determine the maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE). The primary objective of the second part of the study (dose expansion) is to further evaluate the safety and efficacy of raludotatug deruxtecan in patients with advanced ovarian cancer and in patients with advanced renal cell carcinoma.

The study will evaluate safety endpoints, including dose-limiting toxicities and adverse events and efficacy endpoints, including objective response rate (ORR), duration of response (DoR), disease control rate (DCR), clinical benefit rate, time to response and progression free survival (PFS). Pharmacokinetic and exploratory biomarker endpoints also will be assessed.

The phase 1 trial enrolled 179 patients in Asia and North America.

REJOICE-Ovarian01 is a global, multicenter, randomized, open-label phase 2/3 trial evaluating the efficacy and safety of investigational raludotatug deruxtecan in patients with platinum-resistant, high-grade ovarian primary peritoneal or fallopian tube cancer, with disease progression following at least one but no more than three prior systemic lines of therapy, including prior treatment with mirvetuximab soravtansine for those with documented high-folate receptor alpha expression. Maintenance therapy (e.g., bevacizumab, poly ADP-ribose polymerase [PARP] inhibitors) is considered part of the preceding line of therapy.

The phase 2 part of REJOICE-Ovarian01 is assessing the safety and tolerability of three doses of raludotatug deruxtecan (4.8 mg/kg, 5.6 mg/kg, or 6.4 mg/kg) to identify the recommended dose for the phase 3 part of the trial. The primary endpoint of the phase 2 part of the trial is ORR as assessed by blinded independent central review (BICR). Secondary endpoints include ORR as assessed by investigator, DoR, PFS and DCR – all assessed by both BICR and investigator – and overall survival (OS).

The phase 3 part of REJOICE-Ovarian01 is assessing the efficacy and safety of raludotatug deruxtecan at the selected dose (5.6 mg/kg) compared to investigator's choice of chemotherapy (paclitaxel, pegylated liposomal doxorubicin, gemcitabine or topotecan). The dual primary endpoints of the phase 3 part of the trial are ORR and PFS as assessed by BICR. Secondary endpoints include PFS and ORR as assessed by investigator, DoR and DCR as assessed by both BICR and investigator, and OS. Pharmacokinetic and biomarker endpoints also will be assessed in both parts of the trial.

REJOICE-Ovarian01 is expected to enroll approximately 710 patients across Asia, Europe, North America, and Oceania.

More than 324,000 women were diagnosed with ovarian cancer worldwide in 2022. The median overall survival for advanced ovarian cancer following recurrence can be as little as two years, with a five-year survival rate of 31.8% for those with distant stage disease.

The introduction of targeted therapies has expanded treatment options and improved survival outcomes for some patients with ovarian cancer, but additional options are needed for patients with tumours that progress on available medicines. Between 70% and 80% of patients diagnosed with advanced ovarian cancer will experience disease progression following standard treatment with platinum-based chemotherapy regimens. For patients who develop platinum-resistant ovarian cancer, defined as disease progression less than six months after completion of last platinum-based chemotherapy, prognosis is particularly poor and treatment options are limited.

CDH6 (human cadherin-6) is a cadherin family protein overexpressed in several cancers, including ovarian tumours. An estimated 65% of patients with ovarian cancer have tumours that express CDH6. In addition, CDH6 expression is observed more frequently in high-grade serous carcinomas. There is currently no CDH6 directed medicine approved for treatment of any cancer.

Raludotatug deruxtecan is an investigational, potential first-in-class CDH6 directed ADC. Designed using Daiichi Sankyo's proprietary DXd ADC Technology, raludotatug deruxtecan is comprised of a humanized anti-CDH6 IgG1 monoclonal antibody attached to a number of topoisomerase I inhibitor payloads (an exatecan derivative, DXd) via tetrapeptide-based cleavable linkers.

Daiichi Sankyo and Merck (known as MSD outside of the United States and Canada) entered into a global collaboration in October 2023 to jointly develop and commercialize patritumab deruxtecan (HER3-DXd), ifinatamab deruxtecan (I-DXd) and raludotatug deruxtecan (R-DXd), except in Japan where Daiichi Sankyo will maintain exclusive rights. Daiichi Sankyo will be solely responsible for manufacturing and supply. In August 2024, the global co-development and co-commercialization agreement was expanded to include gocatamig (MK-6070/DS3280), which the companies will jointly develop and commercialize worldwide, except in Japan where Merck & Co., Inc., Rahway, N.J., USA will maintain exclusive rights. Merck & Co., Inc., Rahway, N.J., USA will be solely responsible for manufacturing and supply for gocatamig.

The Daiichi Sankyo ADC portfolio consists of seven ADCs in clinical development crafted from two distinct ADC technology platforms discovered in-house by Daiichi Sankyo.

The ADC platform furthest in clinical development is Daiichi Sankyo's DXd ADC Technology where each ADC consists of a monoclonal antibody attached to a number of topoisomerase I inhibitor payloads (an exatecan derivative, DXd) via tetrapeptide-based cleavable linkers. The DXd ADC portfolio currently consists of Enhertu, a HER2 directed ADC, and Datroway, a TROP2 directed ADC, which are being jointly developed and commercialized globally with AstraZeneca. Patritumab deruxtecan (HER3-DXd), a HER3 directed ADC, ifinatamab deruxtecan (I-DXd), a B7-H3 directed ADC, and raludotatug deruxtecan (R-DXd), a CDH6 directed ADC, are being jointly developed and commercialized globally with Merck & Co., Inc.,

Rahway, N.J., USA. DS-3939, a TA-MUC1 directed ADC, is being developed by Daiichi Sankyo.

The second Daiichi Sankyo ADC platform consists of a monoclonal antibody attached to a modified pyrrolobenzodiazepine (PBD) payload. DS-9606, a CLDN6 directed PBD ADC, is the first of several planned ADCs in clinical development utilizing this platform.

Ifinatamab deruxtecan, patritumab deruxtecan, raludotatug deruxtecan, DS-3939 and DS-9606 are investigational medicines that have not been approved for any indication in any country. Safety and efficacy have not been established.

Daiichi Sankyo is an innovative global healthcare company contributing to the sustainable development of society that discovers, develops and delivers new standards of care to enrich the quality of life around the world.

News Source:

https://www.pharmabiz.com/NewsDetails.aspx?aid=181282&sid=2