Short Communication

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FDA approves Datroway: a novel therapy for HR-positive, HER2-negative metastatic breast cancer

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Abstract

The Food and Drug Administration (FDA) has approved datopotamab deruxtecan (Datroway) for the treatment of unresectable or metastatic HR-positive, HER2-negative breast cancer. This antibody–drug conjugate comprises a monoclonal antibody (mAb) that targets TROP2, a cytotoxic agent DXd, and a linker. The mAb binds to TROP2 on cancer cells, facilitating internalization, after which DXd is released, inducing cell death. In the TROPION-Breast01 trial, datopotamab deruxtecan demonstrated superiority over conventional chemotherapy. It provides a promising alternative for patients who have failed prior endocrine or chemotherapy, offering enhanced efficacy than traditional treatments. However, additional studies are required to thoroughly assess the drug's safety and efficacy, as well as to establish the most current information regarding its optimal dosage and administration guidelines.

Keywords: breast cancer, chemotherapy, datopotamab deruxtecan, Datroway, oncology

On 17 January 2025, the U.S. Food and Drug Administration (FDA) granted approval for Datroway (datopotamab deruxtecan), a conjugate comprising a Trop-2-targeted antibody and a topoisomerase inhibitor, for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (IHC0, IHC1+, or IHC2+/ISH–) breast cancer. This approval specifically applies to individuals who have previously undergone endocrine-based therapy and chemotherapy for unresectable or metastatic disease[1].

Breast cancer remains the most prevalent malignancy among women worldwide. In 2022, an estimated 1.3 million new cases were recorded, resulting in 666 103 deaths[2]. Mortality rates are disproportionately higher in transitioning regions, including Melanesia, Western Africa, Micronesia/Polynesia, and the Caribbean, where the incidence rate is approximately 88% greater than in transitioned regions such as Australia/New Zealand, Western Europe, Northern America, and Northern Europe[3]. This disparity may be attributed to limited access to early detection, inaccessibility of advanced treatment, and poor healthcare infrastructure in transitioning countries.

Risk factors for breast cancer can be categorized into non-modifiable factors (e.g., age, genetics, and early menstruation) and modifiable factors (e.g., obesity, physical inactivity, late pregnancy, and alcohol consumption)[4]. Approximately, 5–10% of breast cancer cases are attributed to inherited genetic mutations. The most common hereditary cause is a mutation in the BRCA1 or BRCA2 genes. Women with a BRCA1 mutation face a 55–65% lifetime risk of developing breast cancer, while those with a BRCA2 mutation have a 45% risk. By the age of 80, the cumulative risk for carriers of either mutation is approximately 70%[5]. Hormonal factors, such as estrogen and progesterone used in contraceptives or hormone replacement therapy, have also been linked to an increased risk of breast cancer[5]. Initially, abnormal cells may develop into non-invasive lesions, such as ductal carcinoma in situ, before progressing to invasive cancer. Tumor growth promotes angiogenesis, facilitating metastasis to organs like the lungs, bones, and liver[6].

Breast cancer is a genetically and clinically diverse disease comprising multiple subtypes. Its classification has evolved, with the most widely accepted system based on immunohistochemical markers, including HR and HER2. This classification identifies four primary subtypes: luminal A, luminal B, HER2-positive, and triple-negative breast cancer (TNBC)[7]. HR-positive tumors express estrogen (ER) and/or progesterone (PR) receptors, making them responsive to hormone therapy, and are categorized into luminal A and B. Luminal A tumors are ER and/or PR positive, with low Ki-67 expression (<20%) and favorable prognosis, while Luminal B tumors are ER positive (and can be PR negative), higher grade, with high Ki-67 expression (>20%). HER2-positive tumors overexpress the HER2 protein, leading to rapid growth but responding well to HER2-targeted therapies. TNBC, lacks ER, PR, and HER2 expression, and is highly aggressive with limited targeted treatments[7,8]. These classifications guide prognosis and treatment strategies.

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Datroway (datopotamab deruxtecan) is an antibody–drug conjugate comprising three components: a monoclonal antibody (mAb) targeting TROP2 (trophoblast cell surface antigen 2) on cancer cells, the cytotoxic agent DXd, and a linker that connects the mAb to DXd. The mAb binds to TROP2 on cancer cells, facilitating internalization. Once inside the cell, DXd is released, inducing cell death by damaging the cancer cells through its cytotoxic effects[9]. The recommended dose of datopotamab deruxtecan is 6 mg/kg (with a maximum of 540 mg for patients weighing 90 kg or more), given as an intravenous infusion every 3 weeks (21-day cycle) until disease progression or intolerable toxicity occurs[1].

The efficacy of Datroway was assessed in the TROPION-Breast01 trial[10], a multicenter, open-label, randomized study (NCT05104866) involving 732 patients with metastatic or unresectable breast cancer who had progressed on prior chemotherapy. Participants were randomized to receive either datopotamab deruxtecan (365 patients) or investigator's choice chemotherapy (367 patients). The primary endpoints were progression-free survival (PFS) and overall survival (OS), with secondary measures including objective response rate (ORR) and duration of response (DOR). Datroway significantly improved PFS (6.9 vs. 4.9 months; HR 0.63, $P< 0.0001$), while median OS was comparable (18.6 vs. 18.3 months). The confirmed ORR was 36% for Datroway versus 23% for chemotherapy, with a DOR of 6.7 versus 5.7 months. Common adverse effects included nausea, fatigue, hair loss, and lung complications[1]. Based on these results, the FDA approved Datroway for HR-positive, HER2-negative metastatic breast cancer, especially where prior endocrine and chemotherapy treatment did not benefit.

The HR-positive, HER2-negative breast cancer treatment poses a particular challenge due to its potentially limited response to conventional treatments. Estrogen receptor modulators and estrogen deprivation have long been established treatments for HR-positive metastatic breast cancer. However, resistance to these therapies often develops after initial benefit, leading to disease progression and complicating treatment outcomes[11]. Datopotamab deruxtecan represents an innovative therapeutic strategy targeting TROP2, a protein often overexpressed in HR-positive, HER2-negative breast cancer, offering a potential treatment option for patients refractory to previous endocrine or chemotherapy regimens. However, further investigation is necessary to rigorously assess its long-term efficacy, safety profile, optimal dosing, and administration protocols, to establish comprehensive clinical guidelines and fully elucidate its therapeutic potential.

Ethical approval

Not required.

Consent

Not required.

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Author's contribution

O.S.: conceptualization, resource allocation, project administration, writing initial draft, reviewing and editing final draft.

Conflict of interest disclosure

The author declares no conflict of interest

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Not invited.

Data availability statement

No new data were generated; hence data sharing is not applicable.

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