

July 24, 2026
Keio University School of Medicine

New Hope for a Rare Skin Cancer: Advanced-Stage Extramammary Paget's Disease

Multi-institutional investigator-initiated trial in Japan confirms favorable efficacy and safety of HER2-targeted antibody-drug conjugate (ADC)

A research group at the Keio University School of Medicine has conducted a multi-institutional, investigator-initiated, phase II clinical trial in Japan (the TEMENOS-2 study; see Note 1). The group was led by Associate Professor Takeru Funakoshi and Assistant Professor Sayuka Arakawa of the Department of Dermatology. The trial evaluated the efficacy and safety of trastuzumab emtansine (T-DM1; see Note 2)—an antibody-drug conjugate (ADC; see Note 3) that targets the protein HER2 (human epidermal growth factor receptor 2; see Note 4) on the surface of cancer cells—in patients with advanced-stage extramammary Paget's disease (EMPD; see Note 5), a rare skin cancer for which no standard treatment has been established.

The trial achieved an objective response rate (the proportion of patients whose tumors shrank) of 92.9%, as assessed by an independent central review committee, demonstrating high therapeutic efficacy along with favorable survival trends and a manageable safety profile. This is the world's first clinical trial to prospectively evaluate the efficacy of a HER2-targeted ADC in advanced-stage extramammary Paget's disease. The findings represent prospective clinical data tumor shrinkage, demonstrating the potential for a new treatment option for patients who have had limited effective systemic chemotherapy options.

These findings were published on July 21, 2026 (Japan time) in *ESMO Open*, the official open-access journal of the European Society for Medical Oncology (ESMO).

1. Research Background

Advanced-stage extramammary Paget's disease (EMPD) is a rare cutaneous malignancy that develops primarily in the genital and perianal regions (e.g., vulva or scrotum) and similar areas in older adults. In the disease's early stages, a cure is often achievable by surgical excision. However, once it metastasizes to other organs or lymph nodes—reaching what is termed the "advanced or metastatic" stage—no evidence-based standard systemic chemotherapy has been established, and the prognosis is extremely poor.

Recent studies have shown that approximately 40% of patients with advanced-stage extramammary Paget's disease overexpress HER2, a protein involved in cancer cell proliferation. This led the researchers to hypothesize that potent HER2-targeted agents such as antibody-drug conjugates (ADCs) might prove effective against advanced-stage extramammary Paget's disease.

However, no prospective clinical trial data had previously been available to verify the efficacy of HER2-targeted ADCs.

The research group therefore initiated a prospective, phase II, investigator-initiated clinical trial (the TEMENOS-2 study; jRCT2031210436) across 11 institutions in Japan to evaluate the efficacy and safety of trastuzumab emtansine (T-DM1)—a HER2-targeted ADC widely used in breast cancer—in patients with HER2-positive metastatic extramammary Paget's disease. The trial was conducted from December 2021 to July 2024.

2. Research Significance and Future Development

The trial enrolled 14 Japanese patients (median age: 65 years) with HER2-positive metastatic extramammary Paget's disease who had not previously received HER2-targeted therapy. Patients received T-DM1 by intravenous infusion every three weeks, with treatment continuing for up to two years. T-DM1 demonstrated favorable efficacy and safety. Key findings are summarized below.

- Tumor shrinkage (objective response rate: 92.9%): As assessed by an independent central review committee, 13 of 14 patients (92.9%) showed marked tumor shrinkage (complete response in 2 patients; partial response in 11).

- Long-term disease control (median progression-free survival: 16.95 months): Median progression-free survival (PFS)—the period during which the disease remained stable without progression—was 16.95 months, representing favorable long-term disease control compared with previous reports. Median overall survival (OS) has not yet been reached, with many patients maintaining long-term survival.
- Favorable safety profile (manageable adverse reactions): No Grade 4 or higher adverse reactions were observed, and an acceptable safety profile was confirmed in a predominantly older patient population (age range: 42–80 years). One patient had treatment interrupted due to mild interstitial lung disease; however, adverse reactions were predictable overall and remained manageable within an outpatient setting.

This study represents a scientifically important achievement in providing prospective clinical trial data demonstrating the efficacy and safety of HER2-targeted ADCs in advanced-stage extramammary Paget's disease—a condition for which treatment options have been extremely limited. The favorable results of this investigator-initiated trial provide clinical insights toward establishing a new treatment option for this rare skin cancer. As efforts advance toward insurance coverage and inclusion in clinical practice guidelines, these findings have the potential to bring new treatment options to patients with extramammary Paget's disease in Japan and worldwide.

3. Additional Information

This study was supported by the Japan Agency for Medical Research and Development (AMED) through its Practical Research for Innovative Cancer Control program, under the project titled "A Multi-Institutional Phase II Investigator-Initiated Clinical Trial to Evaluate the Efficacy and Safety of Trastuzumab Emtansine (T-DM1) Therapy in HER2-Positive Advanced or Recurrent Extramammary Paget's Disease (TEMENOS-2)." The study drug was provided by Chugai Pharmaceutical Co., Ltd.

4. Research Paper

Title : Efficacy and safety of trastuzumab emtansine in patients with advanced human epidermal growth factor receptor 2-positive extramammary Paget's disease: An investigator-initiated, open-label, single-arm, multicentre, prospective, phase II clinical trial (TEMENOS-2)

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Journal : *ESMO Open* (Original Article / Skin Cancers)

DOI : <https://doi.org/10.1016/j.esmoop.2026.108282>

[Glossary]

(Note 1) **Investigator-initiated clinical trial:** A clinical trial planned, designed, and conducted by a physician under their own responsibility, as distinct from conventional industry-sponsored trials. Investigator-initiated trials are often undertaken for rare diseases and other conditions

(Note 2) **Trastuzumab emtansine:** An antibody-drug conjugate (ADC) that targets HER2 on cancer cells to deliver its cytotoxic payload efficiently. Trastuzumab emtansine is approved for breast cancer and certain other indications but is not currently approved in Japan for advanced-stage extramammary Paget's disease (and is therefore not covered by national health insurance). This study was conducted as an investigator-initiated clinical trial.

(Note 3) **Antibody-drug conjugate (ADC):** A novel class of therapy that combines an antibody—which binds to a specific marker on cancer cells (in this case, HER2)—with a potent cytotoxic agent. By delivering the cytotoxic payload directly to targeted cancer cells, ADCs offer enhanced efficacy while minimizing damage to healthy cells (side effects).

(Note 4) **HER2 (human epidermal growth factor receptor 2):** A protein present on the cell surface. When overexpressed in cancer cells, it accelerates cell proliferation. HER2 is an important therapeutic target in breast and gastric cancer and is also expressed in some cases of extramammary Paget's disease.

(Note 5) **Advanced-stage extramammary Paget's disease (EMPD):** A rare adenocarcinoma (a type of skin cancer) that develops primarily in older adults in areas of skin rich in apocrine sweat glands, such as the external genital area (genitals), the perianal region, and the axillae (armpits).

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