

**Ono Announces ONO-4578 (EP4 antagonist) in Combination with Opdivo
and Chemotherapy Met the Primary Endpoint
in a Phase 2 Clinical Trial in Patients with Certain Gastric Cancer**

- ONO-4578, an EP4 antagonist, in combination with Opdivo and chemotherapy demonstrated a significant prolongation of progression-free survival compared with placebo in combination with Opdivo and chemotherapy, meeting the primary endpoint
- The Phase 2 clinical trial was conducted in Japan, South Korea, and Taiwan in patients with previously untreated, HER2-negative unresectable advanced or recurrent gastric cancer (including gastroesophageal junction cancer)

Osaka, Japan, October 9, 2025 – Ono Pharmaceutical Co., Ltd. (Headquarters: Osaka, Japan; President and COO: Toichi Takino; "Ono") announced that ONO-4578, an EP4 antagonist, in combination with Opdivo, an anti-PD-1 antibody and chemotherapy which is one of the standard treatments in this setting met the primary endpoint in the Phase 2 clinical trial ([ONO-4578-08 study](#)) in patients with previously untreated, HER2-negative unresectable advanced or recurrent gastric cancer (including gastroesophageal junction cancer).

In the trial, ONO-4578 in combination with Opdivo and chemotherapy demonstrated a statistically significant prolongation of progression-free survival (PFS) compared with placebo in combination with Opdivo and chemotherapy. In addition, no new safety concerns were identified in the trial. Ono will publish the results at an upcoming academic meeting.

About ONO-4578-08 study

ONO-4578-08 study is a multicenter, randomized Phase 2 clinical trial, conducted in Japan, South Korea and Taiwan in patients with previously untreated, HER2-negative unresectable advanced or recurrent gastric cancer or gastroesophageal junction cancer. ONO-4578 in combination with Opdivo and chemotherapy (S-1 + oxaliplatin or capecitabine + oxaliplatin) was compared with placebo in combination with Opdivo and chemotherapy. In this trial, patients received 40 mg of ONO-4578 once daily and 360 mg of Opdivo every 3 weeks in combination with chemotherapy until disease progression or unacceptable toxicity was observed. The primary endpoint of this trial is PFS.

About Gastric cancer

It is estimated that approximately 126,000 new cases with gastric cancer are diagnosed per year in Japan¹⁾ (approximately 968,000 cases worldwide²⁾) and approximately 43,000 deaths per year in Japan¹⁾ (approximately 660,000 deaths worldwide²⁾) resulting from gastric cancer, which is the third most common type of cancer following colorectal cancer and lung cancer in Japan. Combination therapies with anti-PD-1 antibody and chemotherapy have been approved for the first-line treatment of HER2-negative unresectable advanced or recurrent gastric cancer as the standard treatment. However, unresectable gastric cancer remains incurable, and a new treatment option is needed for patients with gastric cancer.

About ONO-4578

ONO-4578 is a selective, oral antagonist of EP4, which is one of the prostaglandin E₂ (PGE₂) receptors, developed by Ono. PGE₂, which is produced by cancer cells, suppresses the action of

cancer immunity through EP4 receptors expressed on various immune cells³⁾⁻⁵⁾. ONO-4578 is expected to exert antitumor effect by suppressing EP4-mediated effects of PGE₂ and by restoring cancer immunity⁶⁾. In the phase 1 clinical trial in patients with unresectable advanced or recurrent gastric cancer (including gastroesophageal junction cancer) after the third- or later-line treatment, a combination therapy with ONO-4578 and Opdivo showed antitumor effect and a manageable safety profile⁷⁾. Currently, Ono is conducting several clinical trials of ONO-4578, including a global phase 2 clinical trial in patients with colorectal cancer.

References:

- 1) Globocan 2022: Stomach Cancer, Japan, World Health Organization Available at:
<https://gco.iarc.who.int/media/globocan/factsheets/populations/392-japan-fact-sheet.pdf>
- 2) Globocan 2022: Stomach Cancer, World, World Health Organization Available at:
<https://gco.iarc.who.int/media/globocan/factsheets/populations/900-world-fact-sheet.pdf>
- 3) Obermajer N, et al. Transplant Res. 2012;1:15.
- 4) Ylöstalo JH, et al. Stem Cells. 2012;30:2283-96.
- 5) Okano M, et al. Immunology. 2006;118:343-52.
- 6) Kotani T, et al. Cancer Res. 2020;80:16_Supplement 4443.
- 7) Kawazoe A, et al. Cancer Sci. 2025;116:2523-36.

Contact:

Ono Pharmaceutical Co., Ltd.
Corporate Communications
TEL:06-6263-5670