

The NCCN Oncology Research Program (ORP) strives to improve the quality of life for patients and reduce cancer-related deaths by advancing cancer therapies through research. Since the program's establishment in 1999, the NCCN ORP has brought millions of dollars in research grants to investigators at NCCN Member Institutions. Research grants are provided to NCCN through collaborations with pharmaceutical and biotechnology companies; these grants are in turn used to support scientifically meritorious cancer research efforts.

NCCN ORP studies typically explore new avenues of clinical investigation and seek answers to important cancer-related questions. All studies are approved and funded through a scientific peer-review process and are overseen by the ORP.

This feature highlights an NCCN study funded through the grant mechanism.

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For more information on specific trials, including patient selection criteria, use the contact information listed with each study.

For more information on the NCCN ORP, including a complete detailing of the clinical studies currently underway at NCCN Member Institutions, go to www.nccn.org/education-research/nccn-oncology-research-program/orp-main-page.

A Multi-Center Phase I Trial of Neratinib and Fam-Trastuzumab Deruxtecan in Patients With Advanced Refractory Gastric Cancer

Principal Investigator: Namrata Vijayvergia, MD

Condition: Gastric adenocarcinoma

Institution: Fox Chase Cancer Center

This is a phase I dose-finding trial with potential dose expansion to evaluate the safety, toxicity, recommended phase II dose (RP2D), and maximum tolerated dose (MTD) of neratinib + fam-trastuzumab deruxtecan (TDxD) using a standard 3 + 3 dose escalation design in patients with metastatic or unresectable gastric adenocarcinoma (including gastroesophageal junction tumors) that are HER2-overexpressing (IHC3+ or IHC2+/ISH+). Patients must have experienced disease progression or been intolerant of at least one prior line of chemotherapy and HER2-directed therapy. A total of 18 patients will be enrolled. It is anticipated that the trials may escalate through 3 different dose levels of neratinib (120 mg, 160 mg, 200 mg). Both drugs have gastrointestinal toxicity, specifically diarrhea, and the combination may have risk of increased toxicity from TDxD due to increased cellular uptake of the cytotoxic payload. If the initial dose level 0 is deemed too toxic, the study investigators and the data and safety monitoring board can decide to allow dose reduction of TDxD to 4.4mg/kg (dose level -1) and re-introduction of neratinib at dose level 0 if the toxicities are felt to be related to TDxD. For cycle 1, patients will start with a neratinib lead-in at day -7 and TDxD will be administered on day 1. Each future treatment cycle will consist of neratinib administered orally daily for a 21-day cycle with food. TDxD will be administered intravenously on day 1 of a 21-day cycle. All patients will undergo screening via transthoracic echocardiography or multigated acquisition (MUGA) scanning prior to initiating treatment and every 9 weeks while on treatment. Tumor assessment must be performed every 3 cycles (± 7 days). The assessment will be conducted before day 1 of each cycle as possible.

Primary Objective:

- Determine the MTD and RP2D of the combination of TDxD + neratinib in patients with metastatic or unresectable HER2-positive gastroesophageal adenocarcinoma

Secondary Objectives:

- Determine the objective response rate (complete response [CR] + partial response [PR]) of TDxD + neratinib
- Determine the disease control rate (CR + PR + stable disease) of TDxD + neratinib
- Determine the progression-free survival of TDxD + neratinib
- Determine the overall survival of TDxD + neratinib
- Define the safety of the combination of TDxD + neratinib, including the rate of grade ≥ 3 adverse events

Exploratory Objective:

- Investigate the emergence of new somatic *HER2* mutations and track *HER2* copy numbers through peripheral blood cell-free DNA analysis using the Guardant360 panel as the marker for response and emergence of resistance

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