Cancer trial discovers a potentially broader role for an established dual HER2-blocking treatment

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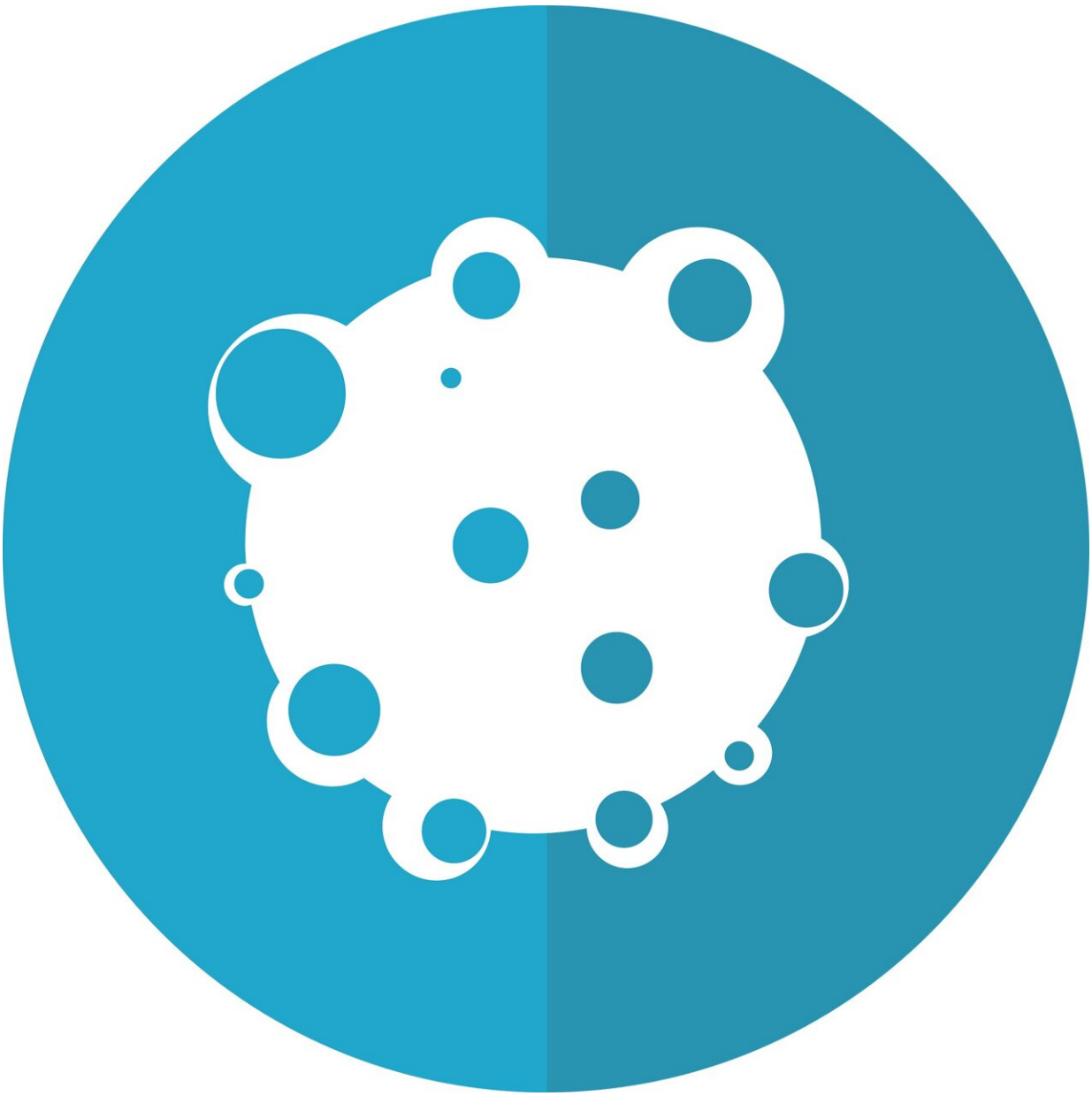

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An important discovery from the NCI-MATCH precision medicine initiative is published in *Clinical Cancer Research*.

Trastuzumab-pertuzumab, a drug combination approved by the US Food and Drug Administration (FDA) to treat patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer, shrunk tumors in patients with several other types of cancer with high levels of the HER2 gene. NCI-MATCH (Molecular Analysis for Therapy Choice) is one of the first and largest precision oncology trials ever undertaken globally.

NCI-MATCH Arm J was a single-arm phase 2 trial in patients with advanced (metastatic) HER2-amplified cancers other than breast cancer. The study also excluded patients with gastric (stomach) cancer or gastroesophageal junction adenocarcinoma, where there is another approved targeted therapy. HER2 receptors control how cells grow and divide.

"This was an extremely important study based on the established efficacy benefits of the trastuzumab-pertuzumab combination in HER2-positive breast cancer. We found that select patients with other cancer types with high levels of HER2 amplification benefitted from this approach, which is associated with minimal side effects," said lead investigator Roisin M. Connolly, MB, BCh, MD, of University College Cork in Ireland, and the ECOG-ACRIN Cancer Research Group (ECOG-ACRIN).

The development of resistance to trastuzumab is a common clinical challenge, leading to numerous clinical trials seeking improvements for patients.

"It is so important for us to identify treatment approaches that result in high rates of tumor shrinkage while minimizing adverse effects for the patients and maximizing quality of life during the treatment course," said Dr. Connolly.

Eligible patients for NCI-MATCH Arm J had high levels of HER2 amplification, defined as a copy number of seven or more. The study enrolled 35 patients, and the primary analysis included 25 based on central evaluation of HER2 amplification. The median age was 66 (range 31-80), 56% were female, and half had three or more prior therapies (range 1-11). The cancer types were gynecologic (11), gastrointestinal (11), urinary bladder (2), and head and neck (1).

"As a number of patients in Arm J had shrinkage of their cancers with this dual HER2 blockade, it is clear that select patients with this genomic aberration may benefit from HER2 pathway blockade," Dr. Connolly explained.

The confirmed overall response rate (ORR) in evaluable patients was 12% (3/25 patients). All three patients had a partial response. They each had a different cancer: adenocarcinoma of the rectum, cholangiocarcinoma, and transitional cell carcinoma of the bladder.

There was one additional partial response in a patient with urothelial cancer and an unconfirmed HER2 copy number. Stable disease was observed in another nine patients with cholangiocarcinoma and gynecologic and colorectal cancers. The trial came just short of meeting the predefined success criteria for the primary endpoint (defined as an ORR greater than 16% or 4/25 patients).

"As the prespecified criteria for efficacy success were not met, it may be that more refined patient selection, such as predictive biomarkers, or alternative HER2-directed approaches, such as combinations with chemotherapy, or newer antibody-drug conjugates, may help a larger proportion of patients," she said.

The NCI sponsored the trial. The manufacturer, Genentech, a member of the Roche Group, supplied trastuzumab-pertuzumab for the trial through a Clinical Trial Participation Agreement with NCI.

More information: Roisin M. Connolly et al, Trastuzumab and Pertuzumab in Patients with non-Breast/Gastroesophageal HER2-amplified Tumors: Results from the NCI-MATCH ECOG-ACRIN Trial (EAY131) Sub-protocol J, *Clinical Cancer Research* (2024). DOI: 10.1158/1078-0432.CCR-23-0633

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