NIH’s ComboMATCH Initiative Will Test New Drug Combinations Guided by Tumor Biology

ComboMATCH comprises numerous clinical trials that will evaluate different drug combinations.

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The National Cancer Institute (NCI) has launched a large precision medicine cancer initiative to test the effectiveness of treating adults and children with new drug combinations that target specific tumor alterations. Known as the Combination Therapy Platform Trial with Molecular Analysis for Therapy Choice (ComboMATCH), the initiative is the largest of its kind to test combinations of cancer drugs guided by tumor biology.

The endeavor aims to identify promising treatments that can advance to larger, more definitive clinical trials outside of ComboMATCH. NCI is part of the National Institutes of Health.

ComboMATCH comprises numerous phase 2 treatment trials that will each evaluate a drug combination—usually either two targeted drugs or a targeted drug plus a chemotherapy drug. Some trials will include patients with specific changes in their cancer cells, no matter where the cancer arose in the body, whereas others will enroll patients with specific cancer types.

“The majority of treatments that patients get nowadays are not genomically determined,” said James H. Doroshow, MD, director of NCI’s Division of Cancer Treatment and Diagnosis. “With ComboMATCH, we’re trying to show that genomic abnormalities can be used to determine the most effective treatment combinations for patients.”

ComboMATCH (NCT05564377) is a cross-group collaboration among NCI and all five U.S. clinical trial groups within NCI’s National Clinical Trials Network (NCTN). ComboMATCH is a successor to NCI-MATCH, NCI’s groundbreaking precision medicine clinical trial. In NCI-MATCH, people were assigned to treatment based on genetic changes in their tumor rather than their type of cancer. For the most part, NCI-MATCH evaluated single drugs targeting the mutation thought to be driving the growth of a patient’s tumor. However, many patients quickly developed resistance to these single drugs.

“With ComboMATCH, we’re hoping that by attacking both the genetic driver and the mechanisms of resistance, we will obtain more durable clinical responses and more benefit to patients,” said

Jeffrey Moscow, MD, of the Investigational Drug Branch in NCI's Division of Cancer Treatment and Diagnosis and a co-leader of ComboMATCH.

The combinations will include both U.S. Food and Drug Administration-approved drugs and investigational agents contributed by pharmaceutical companies. Hundreds of thousands of potential drug combinations exist, so one challenge has been to narrow down and prioritize the most promising ones.

The overarching ComboMATCH coordination effort is led by the ECOG-ACRIN Cancer Research Group. All five U.S. NCTN groups, which include the Alliance for Clinical Trials in Oncology, Children's Oncology Group, ECOG-ACRIN Cancer Research Group, NRG Oncology, and SWOG Cancer Research Network, will lead ComboMATCH treatment trials.

"An important strength of the study is that the combinations being evaluated in ComboMATCH will be based on preclinical data showing that indeed the combination is better than either agent alone, as well as safety data from phase 1 studies," said James Ford, MD, of Stanford University School of Medicine, a co-leader of ComboMATCH and lead investigator on the coordination effort by ECOG-ACRIN. "There will be agreement among all the NCTN trial group representatives to evaluate each combination."

There are several ways in which patients with locally advanced or metastatic solid tumors will be identified for possible participation in ComboMATCH. In recent years, genomic testing of tumors has become a standard part of care for people with many cancer types. A doctor at any of the community hospitals and cancer centers participating in ComboMATCH can refer their patient for additional eligibility screening if the patient's test results show that they have a particular alteration being investigated in one of the treatment trials. Any one of the nearly 35 designated commercial and academic labs that are conducting genomic testing as part of standard of care can also identify patients who might be eligible for a ComboMATCH trial.

Patients who are matched to a trial will be asked to provide a pretreatment tumor biopsy specimen for genomic profiling. This will enable ComboMATCH investigators to later probe other questions, such as why some treatments worked and others didn't.

Three ComboMATCH trials are already open for enrollment:

- A study testing the use of fulvestrant (Faslodex) and binimetinib (Mektovi) in patients with an NF1 mutation in hormone receptor-positive breast cancer that has spread (NCT05554354)
- A study testing the use of selumetinib (Koselugo) and olaparib (Lynparza) or selumetinib alone in women with a RAS mutation who have endometrial or ovarian cancer that has come back or persists despite treatment (NCT05554328)
- A study of chemotherapy plus ipatasertib in patients with AKT mutations who have solid tumors

that have spread (NCT05554380)

Six additional trials will be available in the coming months, with more to be added over time. Overall, NCI plans for ComboMATCH to include about 2,000 patients, but that number could grow.

Unlike MATCH, which did not include children, but rather had a separate parallel trial called PediatricMATCH, some ComboMATCH trials will include children with cancer.

NCI will be launching two additional precision medicine cancer treatment trials. ImmunoMATCH has started with a pilot study to determine how prospective characterization of the immune status of a tumor can be used to improve the response to targeted treatments using immunotherapy, with plans to expand into larger studies in the future. MyeloMATCH will test treatments based on genetic changes in the cancer cells of people with acute myeloid leukemia or myelodysplastic syndromes.

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