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**NCI-MATCH (*NCI-Molecular Analysis for Therapy Choice*): Questions and Answers**

**1. What is the NCI-MATCH trial?**

The NCI-Molecular Analysis for Therapy Choice (NCI-MATCH) trial is a clinical trial that will analyze patients' tumors to determine whether they contain genetic abnormalities upon which a drug could have an effect (termed "actionable mutations") and assign treatment based on which abnormality is present. NCI-MATCH seeks to determine whether treating cancers according to their molecular abnormalities will show evidence of effectiveness. As a master protocol, or umbrella trial, NCI-MATCH can add new treatments or drop treatments over time. The trial will initially have 10 arms, each of which will enroll patients to a specific molecularly targeted treatment. To be eligible for the study, participants must have an advanced solid tumor or lymphoma that is no longer responding (or never responded) to standard therapy and has begun to grow.

**2. Will rare cancers be a part of the trial?**

One goal of the trial is for at least 25 percent of the 1,000 patients enrolled to have rare cancers, which can include cancers at anatomic sites in the body in which cancer rarely occurs, such as the eye, the ureter, and the pituitary gland, as well as other cancers that are classified as rare because their specific anatomic location at the time of diagnosis cannot be determined due to the advanced stage of the tumor. For this trial, common cancers are defined as non-small cell lung, prostate, breast, or colorectal cancer.

**3. How will the trial work?**

The NCI-MATCH trial has two enrollment steps. Each patient will initially enroll for screening in which samples of their tumor will be removed (biopsied). The samples will undergo DNA sequencing to detect genetic abnormalities that may be driving tumor growth and might be targeted by one of a wide range of drugs being studied. If a molecular abnormality is detected for which there is a specific substudy available, to be accepted in NCI-MATCH patients will be

further evaluated to determine if they meet the specific eligibility requirements within that arm. Once enrolled, patients will be treated with the targeted drug regimen for as long as their tumor shrinks or remains stable. Overall, trial investigators plan to screen about 3,000 patients during the full course of the NCI-MATCH trial to enroll about 1,000 patients in the various treatment arms. Each arm will include approximately 35 patients. It is important to note that assignment to treatment will be based on the genetic abnormality that is thought to be driving a participant's cancer, not on their type of cancer.

Patients whose tumors do not have genetic alterations that are targeted by the drugs being tested in the trial will have their molecular screening results sent to their doctors. Their doctors may be able to use these results to investigate other clinical trials or treatments for the patient.

#### **4. Why is NCI-MATCH necessary?**

The effectiveness of a therapy targeted against a mutant protein that drives the growth of a cancer was first demonstrated in the year 2000. The drug developed, imatinib (Gleevec®), targets a protein known as the BCR-ABL tyrosine kinase, which drives the growth of most chronic myelogenous leukemias. Since that finding, increasing attention has been focused on developing targeted therapies that act against the many altered proteins that can drive cancer. In most successful applications of molecularly targeted therapies, such as the use of EGFR and ALK inhibitors in non-small cell lung cancer, and BRAF inhibitors in melanoma, researchers learned that it was necessary to pre-screen tumors to ensure the presence of the targeted genetic alteration.

Most recently, efforts to catalog driver mutations across over 30 different types of cancer in The Cancer Genome Atlas (TCGA) project have shown that only a small proportion of patients with any particular cancer type have a specific driver mutation. It is estimated that up to 10,000 patients with any given histologic (based on how the tumor cells look under the microscope) type of cancer would need to be screened to capture the true prevalence of the rarer mutations. Most of the known driver mutations that may have active treatments are found in only 2 percent to 8 percent of patients across all types of cancer – and there are more than 100 types of cancer. Thus, to efficiently investigate the effectiveness of molecularly targeted therapies for patients with the corresponding driver mutations, a broad-based genomic pre-screening effort is necessary to find and assign patients whose tumors harbor these mutations, regardless of tumor origin.

There also is evidence that treatments directed at driver mutations can work across multiple tumor types that share common driver mutations, as well as evidence that some targeted treatments work better in some tumor types than others, even if the same mutation is present (e.g., BRAF inhibitors work well in melanoma with the BRAF-V600E mutation, but not in colon tumors with the same mutation). Because it is difficult to perform molecularly targeted clinical trials except in the most prevalent types of cancers, NCI-MATCH is designed to be able to detect responses to the inhibition of driver mutations in more than one tumor type. Such findings can then be followed up with additional clinical trials to ascertain patient benefit.

## **5. How will investigators know if a treatment tested in NCI-MATCH is beneficial?**

The primary endpoint in the NCI-MATCH trial will be overall response rate (ORR), which is the proportion of patients who have their tumor disappear or shrink. Tumor disappearance is called a complete response. By comparison, partial response has varying standard definitions for different types of tumors. For example, for most solid tumors, partial response is defined as tumor shrinkage (as measured by thickness, width, or length of the tumor) of 30 percent or more over a defined period of time. Treatments in NCI-MATCH will be considered promising if at least 5 out of 31 patients (16 percent) are observed to have at least a partial response to the treatment.

A secondary endpoint is six-month progression-free survival (PFS) which is the percentage of patients whose disease does not worsen for at least six months. Investigators will also assess time to progression (the length of time a patient lives before their disease worsens) and evaluate toxicities seen during treatment. For those patients who finish their treatment in the study, their personal doctor will continue to monitor them for side effects and follow their condition for the subsequent five years.

Patients whose cancers progress during the first assigned treatment may be able to go onto another NCI-MATCH trial arm if they have a second molecular target in their tumors that can be treated with an available drug. In addition, any patient whose cancer initially shrinks and later progresses during the trial will be eligible to have their tumors re-biopsied and, if they have a genetic change that is targeted by another drug being tested in NCI-MATCH, they may be eligible to enroll in one of the other arms.

## **6. Is there risk in having biopsies taken for genetic analysis?**

Most biopsies should be low-risk. Biopsies should be able to be performed with less than a 2 percent risk of serious complications. Eligible patients must have a tumor that is reachable by a biopsy needle in order to have a sample examined. During the procedure, the doctor will insert a small needle into the tumor, guided by an X-ray or other imaging technique. Biopsies could also be performed during a planned and clinically necessary surgical procedure or endoscopy as part of their treatment for cancer or other health condition, but these types of procedures would not be done solely to obtain a biopsy specimen. A sample of the tissue will be removed and sent to a lab where DNA from the tissue will be analyzed for mutations being studied in this trial.

The tumor sample must be obtained after any other treatment the patient received prior to consideration for NCI-MATCH (archived specimens after which treatment was given will not be eligible), and the patient must have received standard treatment and then had their cancer grow in order to be eligible for NCI-MATCH. Patients must also have adequate liver, blood, and kidney function and be able to perform normal activities of living.

When a patient is told “your tumor has progressed,” it usually takes up to a week to schedule a biopsy and an additional 14 days for the genetic testing. This is the normal turnaround time for any tumor biopsy and molecular result.

**7. Who is performing the molecular analysis, and how is the process being standardized?**

Once a biopsy specimen is processed, it is then sent to a genetic testing lab where technicians will examine the specimen for more than 4,000 different variants across 143 genes. By comparison, the Lung-MAP trial, an NCI National Clinical Trials Network (NCTN) trial that was launched in 2014, is analyzing about 3,000 variants. All genetic testing will be performed using a standardized process in one of four Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories:

- MD Anderson Cancer Center Molecular Diagnostics NGS Laboratory  
Massachusetts General Hospital Center for Integrated Diagnostics
- Molecular Characterization Laboratory at the NCI Frederick National Laboratory for Cancer Research, operated by Leidos Biomedical Research Inc. for the National Cancer Institute, Frederick, Maryland
- Yale University Tumor Profiling Laboratory, New Haven, Connecticut

The results of these tests will be given to the patient's physician in the hope that the information may be useful if there is a need for future treatment.

**8. What are the “actionable mutations” being considered in NCI-MATCH and their matching drugs?**

The genetic test will assess certain molecular abnormalities, but additional mutations and treatments are expected to be added to NCI-MATCH. The first ten arms of the trial will include these agents and molecular targets:

<b>Agent(s)</b>	<b>Molecular Target(s)</b>	<b>Estimated Mutation Prevalence</b>
Crizotinib	ALK rearrangement	4%
Crizotinib	ROS1 translocations	5%
Dabrafenib and Trametinib	BRAF V600E or V600K mutations	7%
Trametinib	BRAF Fusions/ Non-V600E/ Non-V600K BRAF mutations	2.8%
Afatinib	EGFR activating mutations	1-4%
Afatinib	HER2 activating mutations	2-5%
AZD9291	EGFR T790M mutations and rare EGFR activating mutations	1-2%
Ado-trastuzumab emtansine	HER2 amplification	5%
VS6063	NF2 loss	2%
Sunitinib	cKIT mutations	4%

## **9. How are the drugs in the study being selected?**

There are three levels of evidence for consideration in selecting drugs that will be used in the trial:

- Level 1: FDA approved as a cancer treatment, with a companion diagnostic test
- Level 2: The drug met a clinical endpoint (ORR or PFS) in previous studies; evidence of target inhibition; there is plausible evidence of a predictive molecular test
- Level 3: The drug demonstrated evidence of clinical activity with evidence of target inhibition; some evidence of a predictive molecular test.

## **10. Are there any benefits or costs to participating in NCI-MATCH?**

If a person is eligible to participate in NCI-MATCH, their health will be followed very closely. Benefits from the trial might include finding a treatment targeted to a genetic abnormality in a person's cancer, an improvement in symptoms related to their cancer, and longer survival. Trial participants will also help researchers identify treatments that may benefit future patients.

Neither the patients nor their health plans/insurance companies will have to pay for any study-related biopsies or the assigned study drug(s) that were matched to the patients' cancer. Unless patients are informed that certain tests are being done at no charge, they or their health plans/insurance companies will need to cover all of the other costs, including the cost of tests, procedures, or medicines to manage any side effects of the biopsy and treatment. Enrollees will not be paid for participation in this study.

## **11. What happens if a patient's cancer progresses during the first assigned treatment?**

Patients whose cancers progress during the first assigned treatment may be able to go on another NCI-MATCH trial arm if they have a second molecular target in their tumors (after having another biopsy) that can be treated with an available drug and a slot is available. Any patient whose cancer initially shrinks and later progresses has the same opportunity to have their tumors re-biopsied and to enroll in one of the other treatment arms if a slot is available.

## **12. What happens if a patient does not have a match after a first biopsy but a treatment becomes available later that would have matched?**

In this circumstance, the doctor should discuss the situation with a principal investigator of NCI-MATCH. If the patient had another treatment since the initial biopsy, a new biopsy sample would be required.

## **13. When will NCI-MATCH be open for patient enrollment?**

On June 1, 2015, NCI and ECOG-ACRIN, one of the NCTN research groups, announced at the annual American Society of Clinical Oncology (ASCO) meeting in Chicago that the trial will open to patient enrollment in July. It will open with 10 substudies, moving quickly to 20 or more. The study parameters for the first 10 arms have been sent to about 2,400 participating sites nationwide for review in preparation for patient enrollment beginning in July. The exact date for

the opening of patient enrollment will be decided shortly after the ASCO meeting. It is anticipated that up to 20 arms will be available for enrollment by autumn of 2015.

#### **14. Who is conducting the trial?**

NCI-MATCH is supported by the National Cancer Institute (NCI), part of the National Institutes of Health (NIH), and is coordinated by the ECOG-ACRIN Cancer Research Group. Personnel from NCI, ECOG-ACRIN, and the other adult trial groups in the NCTN—the Alliance for Clinical Trials in Oncology, SWOG, and the NRG Oncology Group—have collaborated in the development of NCI-MATCH and are participating in the component trials. The NCTN includes researchers, physicians, and health care professionals at public and private institutions across the United States. They conduct clinical trials on all types of adult cancers. For clinical trial tracking purposes, the trial is also referred to as EAY131. A pediatric version of NCI-MATCH, involving the Children's Oncology Group (COG), another NCTN group, is being planned and is expected to launch later in 2016.

In addition to the institutions belonging to the NCTN, NCI-MATCH will be open to all institutions and sites that participate in the NCI Community Oncology Research Program (NCORP), bringing the total of possible institutions to nearly 2,400 nationwide.

#### **15. Who are the device and pharmaceutical partners for the trial?**

In the first 10 arms of the trial, these will be the pharmaceutical partners, many of which have locations worldwide:

- Novartis
- Pfizer
- Verastem
- Boehringer Ingelheim
- AstraZeneca, Wilmington

For subsequent arms, these are some of the planned pharmaceutical partners but there are ongoing discussions with other companies:

- GSK
- Genentech
- Millenium-Takeda
- Bristol-Myers Squibb

The device manufacturer for the DNA analytics is Thermo Fisher Scientific, Inc. The device employs a targeted sequencing approach using Ion Torrent next-generation sequencing technology to reduce the inherent risk of tumor sample consumption before a meaningful result is obtained. It also enables accurate and reliable genetic variant analysis from samples due to low DNA input requirements (10 nanograms) and fast turnaround times that reduce the time of sample to result.

## **16. How does NCI-MATCH align with the President's Precision Medicine Initiative?**

The Precision Medicine Initiative (PMI) will be funded through a \$215 million request in the President's 2016 Budget for the NIH, the FDA, and the Office of the National Coordinator for Health Information Technology. The PMI revolves around precision medicine, an approach to disease prevention and treatment that takes into account individual differences in people's genes, environments, and lifestyles. Precision medicine will generate tools for clinicians to better understand the complex mechanisms underlying a patient's health, disease, or condition, and to better predict which treatments will be most effective.

The PMI budget request includes \$70 million for NCI to scale up efforts to identify genomic drivers in cancer and apply that knowledge to develop more effective approaches to cancer treatment. NCI-MATCH supports the overall initiative, and is an example of how NCI will accelerate the design and testing of tailored treatments for cancer by expanding genetically based clinical cancer trials, exploring fundamental aspects of cancer biology, and establishing a national "cancer knowledge network" that will generate and share new knowledge to fuel scientific discovery and guide treatment decisions.

## **17. What are umbrella trials and how does NCI-MATCH fit in?**

Umbrella trials are trials that incorporate a variety of tumor types and/or drugs into their design. By contrast, conventional phase II trials usually focus on just one tumor type and one drug (or a combination of drugs). With the advent of targeted therapies, umbrella trials are becoming more common because they can allow the potential benefit of such drugs to be assessed efficiently in many types of tumors. Umbrella trials can study single drugs or combinations of targeted drugs, or they can combine targeted therapies with a standard chemotherapy agent.

## **18. How is NCI-MATCH different from other cancer clinical trials?**

NCI-MATCH will have national reach and will be open at up to 2,400 clinical sites across the United States, whereas most other trials are conducted at only a few sites. Therefore, patients may not need to travel far from home to enroll in the trial. The trial also employs the expertise of the NCI and of specialized investigators and scientists within NCI-Designated Cancer Centers and networks who are at the cutting edge of precision oncology, as well as clinical oncology practices that are experienced in clinical trials.

NCI-MATCH uses an advanced DNA sequencing test that has been extensively validated across four CLIA-certified laboratories for high consistency of results. The investigators in the chosen laboratories are among those with the most expertise in these types of assays. The assay used in the study builds on a commercially available assay from Thermo Fisher Scientific Inc., Waltham, Massachusetts, which has contributed expertise to improve the assay. It also uses standard procedures for the collection of specimens and for preparing specimens for analysis.

The trial will also have many more drugs available than would be available in a single center or in studies launched by pharmaceutical companies. Many pharmaceutical companies are collaborating in NCI-MATCH and have also contributed their expertise. NCI-MATCH is designed as a signal-finding study, that is, to find evidence that a particular drug shows evidence of effectiveness in patients whose tumors carry a particular genetic alteration. If signals are

found, there will be an opportunity to follow up positive results using the extensive clinical sites that are optimized for screening for rare mutations.

#### **19. Will there be a similar trial for those under 18 years of age?**

The NCI-MATCH trial will also have a pediatric counterpart that will enroll children with advanced cancers that have progressed on standard therapy. As in the adult NCI-MATCH trial, DNA sequencing will be used to identify children whose tumors have a genetic abnormality for which either an approved or investigational targeted therapy exists. Known as Pediatric MATCH, this trial is a key element of NCI's Precision Medicine Initiative, which is a component of the NCI proposed budget for FY 2016.

NCI is working with numerous pharmaceutical companies to make the same drugs available for Pediatric MATCH that will be offered in the adult NCI-MATCH trial. Pediatric MATCH, which will be led by the NCI-supported NCTN Children's Oncology Group, is still under development but is expected to launch in 2016.

#### **20. What can patients do if they are interested in finding out more about this trial?**

To learn more, patients should start by speaking with their doctors or healthcare team.

Patients, families, and clinicians can also call the NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237 and English- and Spanish-speaking cancer information specialists can assist. LiveHelp is available Monday-Friday, 8:00 AM - 11:00 PM Eastern Time at [https://livehelp.cancer.gov/app/chat/chat\\_landing](https://livehelp.cancer.gov/app/chat/chat_landing). LiveHelp is available in English only but Spanish information can be found at <http://www.cancer.gov/espanol/global/contactenos>.

Visit NCI's website at <http://www.cancer.gov/nci-match> or the ECOG-ACRIN website at [www.ecog-acrin.org](http://www.ecog-acrin.org)

For a press release on NCI-MATCH, go to <http://www-new.cancer.gov/news-events/press-releases/2015/nci-match>.

For Spanish translations of this press release and Q&A, go to <http://www.cancer.gov/espanol/noticias/comunicados-de-prensa/2015/nci-match>.

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The National Cancer Institute leads the National Cancer Program and the NIH's efforts to dramatically reduce the prevalence of cancer and improve the lives of cancer patients and their families, through research into prevention and cancer biology, the development of new interventions, and the training and mentoring of new researchers. For more information about cancer, please visit the NCI Web site at <http://www.cancer.gov> or call NCI's Cancer Information Service at 1-800-4-CANCER.

The ECOG-ACRIN Cancer Research Group is a membership-based scientific organization that designs and conducts cancer research involving adults who have or are at risk of developing cancer. ECOG-ACRIN comprises nearly 1,100 member institutions in the United States and around the world. Approximately 12,000 physicians, translational scientists, and associated



research professionals from the member institutions are involved in Group research, which is organized into three scientific programs: Cancer Control and Outcomes, Therapeutic Studies, and Biomarker Sciences. ECOG-ACRIN is a Network Group in the NCI NCTN and a Research Base in the NCI NCORP. It is headquartered in Philadelphia, Pa. For more information, visit <http://ecog-acrin.org> or call 215-789-3631.