









The Molecular Analysis for Therapy Choice (NCI-MATCH) Trial: Lessons for Genomic Trial Design

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Abstract

Background: The proportion of tumors of various histologies that may respond to drugs targeted to molecular alterations is unknown. NCI-MATCH, a collaboration between ECOG-ACRIN Cancer Research Group and the National Cancer Institute, was initiated to find efficacy signals by matching patients with refractory malignancies to treatment targeted to potential tumor molecular drivers regardless of cancer histology. **Methods:** Trial development required assumptions about molecular target prevalence, accrual rates, treatment eligibility, and enrollment rates as well as consideration of logistical requirements. Central tumor profiling was performed with an investigational next-generation DNA-targeted sequencing assay of alterations in 143 genes, and protein expression of phosphatase and tensin homolog, mutL homolog 1, mutS homolog 2, and RB transcriptional corepressor 1. Treatments were allocated with a validated computational platform (MATCHBOX). A preplanned interim analysis evaluated assumptions and feasibility in this novel trial. **Results:** At interim analysis, accrual was robust, tumor biopsies were safe (<1% severe events), and profiling success was 87.3%. Actionable molecular alteration frequency met expectations, but assignment and enrollment lagged due to histology exclusions and mismatch of resources to demand. To address this lag, we revised estimates of mutation frequencies, increased screening sample size, added treatments, and improved assay throughput and efficiency (93.9% completion and 14-day turnaround). **Conclusions:** The experiences in the design and implementation of the NCI-MATCH trial suggest that profiling from fresh

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tumor biopsies and assigning treatment can be performed efficiently in a large national network trial. The success of such trials necessitates a broad screening approach and many treatment options easily accessible to patients.

New anticancer agents are increasingly developed in biomarker-defined populations, requiring prospective molecular definition of the cancers hypothesized to be most responsive. Examples include receptor tyrosine-protein kinase *erbB-2* (*ERBB2*) amplified breast cancer, where a 20–25% *ERBB2* amplification rate (1,2) made prospective molecular screening essential for demonstration of trastuzumab efficacy (3). Likewise, for advanced lung adenocarcinoma containing activating epidermal growth factor receptor (*EGFR*) mutations, or anaplastic lymphoma kinase (*ALK*) and proto-oncogene tyrosine-protein kinase *ROS* (*ROS*) fusions, the benefit demonstrated with inhibitors of these pathways in most patients with the appropriate alterations was unequivocal (4–7).

Whether targeted therapies known to be effective in some tumor histologies might exhibit similar effectiveness in other tumor histologies in which they have not yet been evaluated is of great interest. Imatinib, for example, approved by the US Food and Drug Administration (FDA) for chronic myelogenous leukemia (defined by breakpoint cluster region protein (*BCR*)-*abelson* murine leukemia viral oncogene homolog 1 (*ABL*) translocation) and gastrointestinal stromal tumor (the majority have proto-oncogene *c-KIT* (*KIT*) mutations), has also been approved for systemic mastocytosis, chronic eosinophilic leukemia, and dermatofibroma protuberans (8–10) based on individual small trials in rare conditions defined by particular molecular alterations. More recently, the FDA approved drugs for certain rare molecular alterations based on trials that included several histologies. For example, the programmed cell death protein 1 (*PD-1*) inhibitor pembrolizumab was approved for any tumor characterized by mismatch repair deficiency (11), and larotrectinib was approved for any metastatic tumor with a tropomyosin receptor kinase (*TRK*) fusion (12). “Basket” trials, in which one drug or a combination is tested in several cohorts, each with a distinct histology in which the molecular alteration is reasonably frequent and sometimes including an “other” cohort for all cancers in which the molecular abnormality is less frequent, have been reported (13). However, for some tumors in which the targeted mutation is very rare, completing even a small study can be challenging (13).

In April 2013, the leaders of the ECOG-ACRIN Cancer Research Group (ECOG-ACRIN) and the National Cancer Institute (NCI) Division of Cancer Treatment and Diagnosis began development of a signal-finding clinical trial to be performed in the National Clinical Trials Network (NCTN) and the National Community Oncology Research Program involving a large screening effort to select patients for treatments targeted to somatic genomic alterations. The trial goal, involving over 1000 academic and community clinical sites in every state and US territory, was to investigate the activity of genomically targeted treatments across common and less common tumor types.

We incorporated as many targeted therapeutics directed to as many gene alterations as possible, though allowing only one treatment in the trial for each alteration. The initial 3000-patient screening accrual goal was calculated to be enough to complete accrual to subprotocols seeking patients with tumors harboring an alteration with prevalence of 1–2% given a projected match rate of 30%. Prevalence projections of somatic alterations were based on data from the Cancer Genome Atlas and the International Cancer Genome Consortium. However,

because these sources focused on primary tumors before treatment and results might not be applicable to patients with refractory metastatic disease, we also reviewed mutation rates observed in various cancers from cBioPortal (<http://www.cbioportal.org/>) and the University of Texas MD Anderson Cancer Center precision medicine effort.

A fresh biopsy was considered essential, because genetic evolution and an altered genomic profile from the time of initial cancer diagnosis might be expected in a refractory population with advanced cancer. Central profiling assays were employed.

The feasibility of accrual, the mix of tumor histologies screened and/or assigned to a targeted treatment in a trial with broad eligibility criteria, the adequacy of biopsies obtained from diverse clinical sites, the rate of eligibility, and enrollment to subprotocols were all difficult to predict. Because of these uncertainties and the need to establish feasibility of the many steps required to enroll a patient on the NCI-MATCH trial in a national network, an interim analysis was planned following accrual of 500 patients to assess trial progress and to make any needed adjustments. Based on the insights from this analysis, study procedures were adjusted substantially so that upon activating additional subprotocols, we improved assignment efficiency and match rate.

Methods

Protocol Design

Several working committees (Supplementary Table 1, available online) developed an overall trial design and flow, chose appropriate eligibility molecular alterations, and evaluated targeted agents. These teams were overseen by a Steering Committee comprised of the chairpersons of each working committee. A parent master screening protocol, EAY131, housed an array of therapeutic Phase II subprotocols addressing gene alteration and drug pairs, with provision for amending all components as needed (Figure 1). The Agents/Genes Selection Working group recruited young investigators from across the NCTN to lead each subprotocol, each having its specific eligibility criteria and consent process. An interim analysis was planned, requiring screening suspension after 500 patients, to evaluate the trial structure, resources, and workflow, and to determine whether the initial projections for patient accrual, disease distribution, alteration detection, and treatment assignment were accurate. The protocol was reviewed and approved by NCI Central Institutional Review Board for Early Clinical Trials as the institutional review board of record (which has an assurance filed with and approved by the US Department of Health and Human Services) for all sites (NCT02465060).

Selection of Drugs and Definition of Eligibility Variants

Single drugs or combinations were evaluated for inclusion if they targeted molecular alterations with an estimated prevalence of at least 1.5% of the population of refractory cancer patients, had a defined phase II dose and met criteria for clinical activity (ie, the drugs had either been approved or had shown clinically significant activity), or at least activity in a single patient with the relevant tumor molecular alteration. Actionable molecular

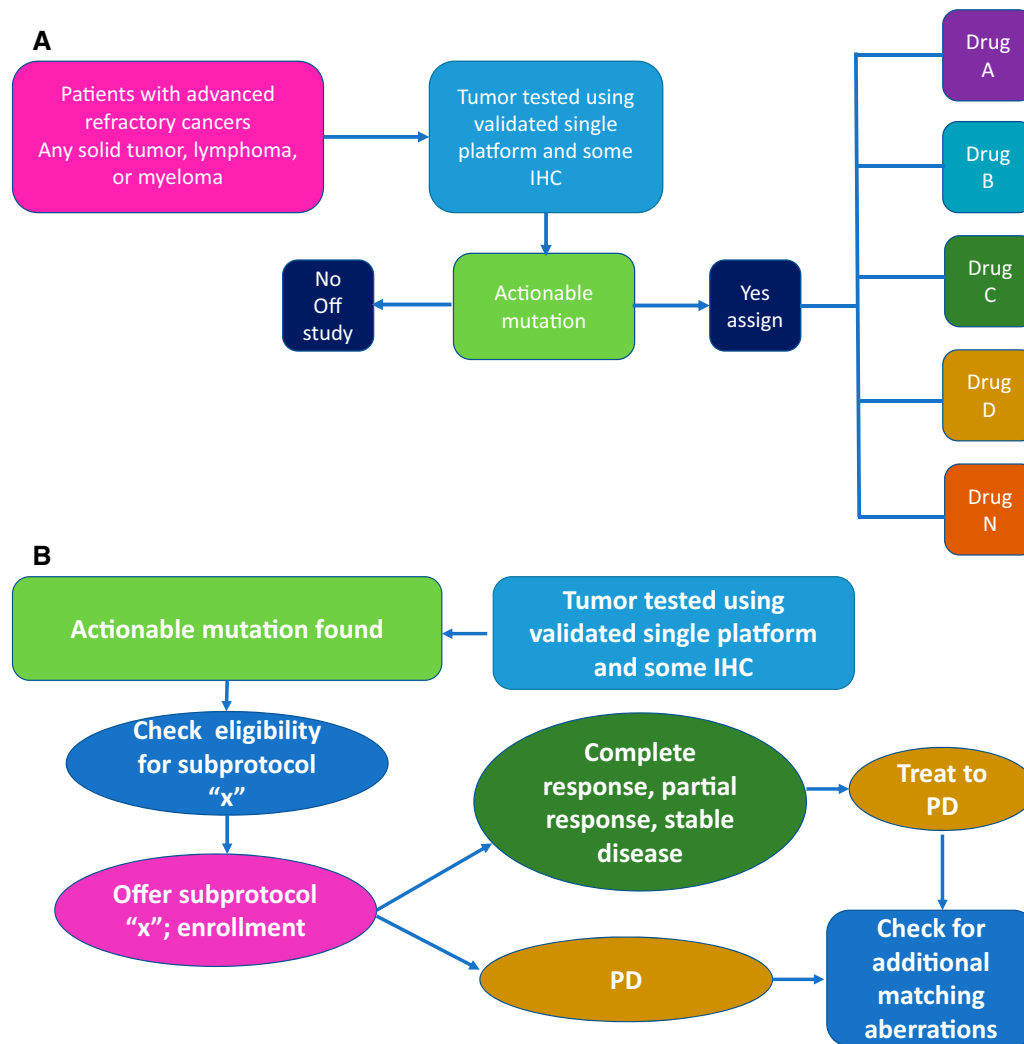


Figure 1. National Cancer Institute (NCI)-MATCH design and patient entry procedures. **A)** NCI -MATCH design (a type of platform trial with features of both umbrella and basket design). **B)** NCI -MATCH procedures for trial entry. IHC = immunohistochemistry; PD = progressive disease.

alterations were those that, at minimum, were associated with preclinical evidence linking the alteration with drug activity.

Patient Selection

Patients eligible for screening were adults with any solid tumor, lymphoma, or myeloma who had progressed on prior treatment or for whom no curative treatment was available and who were willing to provide a tissue biopsy for profiling. Patients were required to have adequate hematopoietic, liver, and kidney function and an Eastern Cooperative Oncology Group (ECOG) performance status of grade 1 or better. Patients were excluded from eligibility to subprotocols if they had a tumor histology in which the drug was approved or in late clinical trial or was known not to be of benefit (4,14). All patients gave written informed consent for the trial.

Tumor Profiling

Patients underwent a biopsy for screening (with an estimated risk of an adverse event <2%), had a clinically indicated biopsy, or, added after the interim analysis, sent a tumor sample from a biopsy obtained within the prior 6 months and after which there

had been no response to treatment. A preaddressed prepaid shipping kit with all required containers, fixatives, blood tubes, and instructions was provided for collection of specimens. Tumor profiling used a validated, targeted Next-generation sequencing (NGS) panel of 143 genes, which assayed single nucleotide variants, indels, amplifications, and selected fusions, and validated immunohistochemistry (IHC) assays for protein expression of phosphatase and tensin homolog (PTEN), mutL homolog 1, and mutS homolog 2 expression (15,16). All assays were performed as investigational assays under an abbreviated Investigational Device Exemption submitted to the NCI's Investigational New Drug Application.

Assignment to Treatment

Patients whose tumors had an actionable alteration were assigned by a prospectively defined, NCI-designed computational platform (MATCHBOX) to one of the available treatment subprotocols (Figure 1). If multiple actionable variants were present, the patient was assigned by the variant with the highest level of evidence, followed by the variant with the highest allele frequency. If still equivalent, assignment was to the subprotocol with the

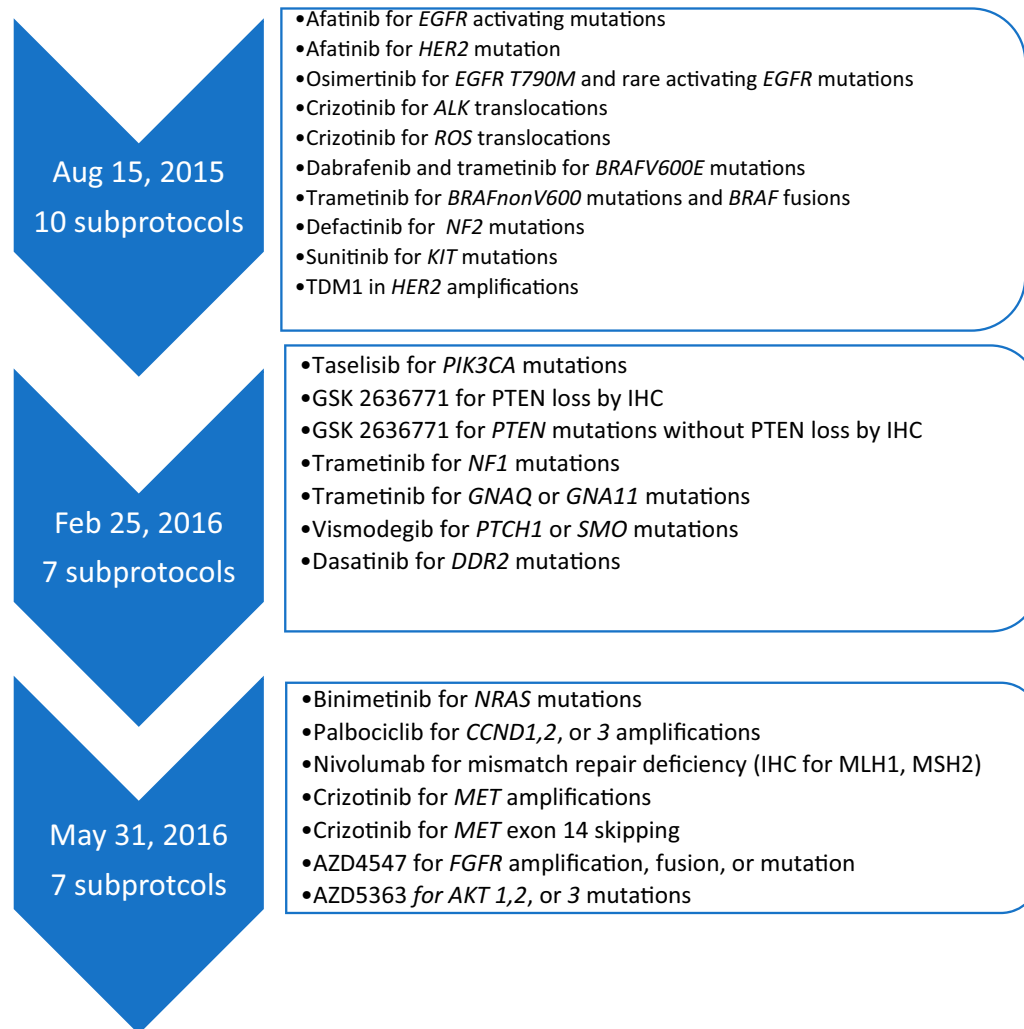


Figure 2. Subprotocol activation timeline for National Cancer Institute (NCI)-MATCH. *EGFR* = epidermal growth factor receptor; *HER2* = human epidermal growth factor receptor 2; *ALK* = anaplastic lymphoma kinase; *ROS* = proto-oncogene tyrosine-protein kinase ROS; *BRAF* = B-Raf proto-oncogene, serine/threonine kinase; *NF2* = neurofibromatosis type 2; *KIT* = KIT proto-oncogene, receptor tyrosine kinase; *PIK3CA* = phosphatidylinositol 3-kinase catalytic subunit; *PTEN* = Phosphatase and tensin homolog; *NF1* = neurofibromatosis type 1; *GNAQ* = G protein subunit alpha q; *GNA11* = Guanine nucleotide-binding protein subunit alpha-11; *PTCH1* = Patched1; *SMO* = Smoothed; *DDR2* = DNA damage response 2; *NRAS* = Rat sarcoma virus GTPase, neuroblastoma; *CCN* = cyclin; *MLH1* = mutL homolog 1; *MSH2* = mutS homolog 2; *MET* = Mesenchymal Epithelial Transition, receptor tyrosine kinase; *FGFR* = Fibroblast Growth Factor Receptor; *AKT* = V-Akt Murine Thymoma Viral Oncogene Homolog.

fewest patients or random if accrual was equal. Patients who progressed after an initial response or had treatment for at least 6 months before progression could have a repeat biopsy for reassignment based on a different actionable alteration. Patients who progressed or stopped their assigned treatment for another reason within 6 months had their original sequencing results reviewed for additional molecular alterations for potential assignment to a second NCI-MATCH subprotocol.

Evaluation of Response

Response was evaluated every two cycles for drugs with a 28-day or 42-day cycle, or every three cycles for drugs with a 21-day cycle using appropriate response criteria (17–20).

Statistical Considerations

NCI-MATCH is a platform trial having features of both umbrella and basket trial designs, planned to screen 3000 patients to

enroll 35 patients on subprotocols with variant prevalence of 1.2% or higher. The primary outcome for NCI-MATCH was the objective response rate for each subprotocol. An interim analysis to examine prevalence and enrollment rates and other assumptions was planned after 500 patients had been screened. In the interim analysis, actual rates computed from the patients already screened were used to project future subprotocol enrollment.

For each subprotocol, a response rate of 5 of 31 patients (16%) was considered promising. Although successful targeted agents often have a response rate of at least 50%, we expected some tumors may be refractory, and a heavily pretreated population may not be as responsive. Secondary objectives included progression-free survival at 6 months, progression-free survival, and toxicity assessment within each subprotocol. The number of subprotocols in the trial depended on the availability and scientific potential of therapies as well as feasibility of accrual, and funding. No single event would trigger the end of screening or accrual to the entire trial.

Results

Accrual

NCI-MATCH opened August 12, 2015, with 10 subprotocols (Figure 2). Patient demographics are shown in Table 1. Community oncology centers registered two-thirds of the patients. By October 2015, at least 500 patients had been accrued; new enrollment was suspended for interim analysis on November 11, 2015, resuming in May 2016. From August 12 to November 11, 2015, 739 tissue specimens were received from 795 registered patients. Screening was much more rapid than the predicted 50 patients per month, averaging 80 specimens per week after 8 weeks.

Although plans were made to restrict common tumors (non-small cell lung cancer, breast cancer, prostate cancer, and colorectal cancer) to 75% of the total, common cancers at interim

analysis comprised only 35.5% of tumors, and 42.4% of those were assigned to subprotocol treatment. The most frequent tumors sequenced were colorectal cancer (13.0%), breast cancer (13.0%), ovarian cancer (11.2%), non-small cell lung cancer (7.4%), pancreatic cancer (5.3%), and head and neck cancer (5.3%) (Table 2).

Molecular Profiling

Molecular profiling was evaluable in 87.3% of tumors (645 patients). Median time from registration to central biopsy receipt was 7 days. The robust accrual overwhelmed the initially planned resources. Median turnaround time from receipt of biopsy to results for assignment increased from 14 days in September 2015 to 36 days in October 2015.

We addressed these issues by three main revisions. First, we implemented a higher throughput NGS platform and increased sample processing personnel. Second, we improved tissue acquisition by allowing submission of clinical biopsies taken within 6 months of registration provided there was no clinical response to any treatment during those 6 months. We strongly recommended a fine needle aspirate simultaneous with the required biopsy—this rescued a proportion of those biopsy specimens that failed to yield usable material. These efforts increased the evaluable molecular profiling rate to 93.9%, decreased the median turnaround time to 14 days, and increased profiling capacity from an expected throughput of 50 per month to 100–150 per week. Finally, we implemented support desks at both the ECOG-ACRIN Operations office for clinical questions and at the central specimen receipt center (University of Texas MD Anderson Cancer Center) for laboratory issues. Educational efforts were increased to reinforce time and biopsy acquisition requirements, including reinforcing the use of provided detailed instructions for sample handling and fixation kits.

Table 1. Patient demographics at interim analysis of NCI-MATCH*

Patient characteristic	Enrolled for screening	Assigned to treatment
	No. (%) (n = 795)	No. (%) (n = 33)
Median age, y (Range)	63 (24–93)	68 (40–82)
Male	305 (38.4)	16 (48.5)
Female	490 (61.6)	17 (51.5)
White	646 (81.27.9)	29 (87.9)
Black	88 (11.1)	1 (3.0)
Asian	27 (3.4)	2 (6.1)
Native American	4 (0.50)	0
Native Hawaiian	1 (0.1)	0
Race not reported	29 (3.6)	1 (3.0)
Hispanic ethnicity	36 (4.9)	0

*NCI = National Cancer Institute.

Table 2. Primary disease sites of patients enrolled for screening at the interim analysis of NCI-MATCH

Cancer type	Enrolled for screening	Screened	Assigned to treatment
	(n = 795) No. (%)	(n = 645) No. (%)	(n = 33) No. (%)
Common cancers			
Colorectal	104 (13.1)	84 (13.0)	6 (18.2)
Breast	96 (12.1)	84 (13.0)	2 (6.1)
Non-small cell lung	62 (7.8)	48 (7.4)	5 (15.2)
Prostate	20 (2.5)	17 (2.6)	1 (3.0)
Common cancers subtotal	282 (35.5)	233 (36.1)	14 (42.4)
Uncommon cancers			
Ovarian	89 (11.2)	72 (11.2)	6 (18.2)
Pancreas (adeno or NOS)	43 (5.4)	34 (5.3)	0
Head and neck*	38 (4.8)	34 (5.3)	0
Endometrial or uterine (nonsarcoma)	34 (4.3)	27 (4.2)	0
Esophageal, GE junction, or gastric	31 (3.9)	28 (4.3)	4 (12.1)
Neuroendocrine†	27 (3.4)	20 (3.1)	2 (6.1)
Cholangiocarcinoma	24 (3.0)	22 (3.4)	1 (3.0)
Bladder or urinary tract	21 (2.6)	14 (2.2)	1 (3.0)
Endometrial or uterine sarcoma‡	20 (2.5)	16 (2.5)	0
Small cell lung	16 (2.0)	14 (2.2)	0
Other§	151 (19.0)	116 (18.0)	3 (9.1)
Primary site not specified	19 (2.4)	15 (2.3)	2 (6.1)
Uncommon cancers subtotal	513 (64.5)	412 (63.9)	19 (57.6)

*Salivary gland (three patients). NCI = National Cancer Institute; NOS = Not Otherwise Specified.

†NOS (18 patients), pancreas (six patients), and carcinoid (three patients).

‡Uterine carcinosarcoma (seven patients).

§Key other types: lymphoma (nine patients), brain tumor (nine patients), and melanoma (nine patients).

Table 3. Actionable alterations: 645 screened patients, initial 10 subprotocols*

NCI-MATCH subprotocol	Assignment rate, %	Estimated prevalence of actionable mutation, %
Q: Ado-trastuzumab emtansine for HER2 amplification	1.7	5
U: Defactinib for NF2 mutations	1.1	2
B: Afatinib for HER2 mutations	0.8	2-6
H: Dabrafenib+trametinib for BRAF V600 mutations	0.8	7
R: Trametinib in BRAF non-V600 mutations	0.3	2.8
E: Osimertinib for EGFR T790M, rare EGFR mutations	0.2	1-2
F: Crizotinib for ALK translocations	0.2	<2
V: Sunitinib for cKIT mutations (non-GIST)	0.2	2
A: Afatinib for EGFR mutations (nonlung)	0	1-4
G: Crizotinib for ROS1 translocations	0	<2

*Table compares the actual assignment rate to the estimated prevalence during protocol design and illustrates that the actual assignment rate is much lower than the initial assumption. ALK = anaplastic lymphoma kinase; BRAF = B-Raf proto-oncogene, serine/threonine kinase; EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor receptor 2; GIST = gastrointestinal stromal tumor; KIT = KIT proto-oncogene, receptor tyrosine kinase; NCI = National Cancer Institute; NF2 = neurofibromatosis type 2; ROS = proto-oncogene tyrosine-protein kinase ROS.

Assignment to Initial 10 Subprotocols

Based on initial assumptions, the anticipated match rate for the first 10 subprotocols was 9%. Of 645 patients' tumors sequenced before interim analysis, 56 (8.7%) had an actionable molecular alteration (Table 3) for one of the open subprotocols. However, due to histology exclusions and other eligibility criteria, only 33 (5.1%) of all patients whose tumors were molecularly screened were eligible for assignment to a subprotocol (Supplementary Figure 1, available online), of which 16 (48.5%) enrolled. Of assigned patients who were not treated, five patients (15.2%) no longer met master protocol eligibility criteria; five patients (15.2%) did not meet subprotocol eligibility criteria; three patients (9.1%) progressed, deteriorated, or started other treatment; and four patients (12.1%) died.

New Estimate of Frequency of Actionable Alterations

Compared with initial assumptions, we observed a lower actionable alteration frequency in the initial 645 patients' tumors (Table 3). The interim analysis allowed more accurate prediction of the potential assignment rate for subsequently added subprotocols (Table 4). After comparing the prevalence of actionable alterations in the 645 patients entered before the interim analysis to the eligibility requirements for the 24 future subprotocols, the expected assignment rate increased to 25.3%, allowing for ineligible histologies and other ineligibility criteria (Table 4). We projected that with 5000 screened patients, our upcoming subprotocols addressing alterations in phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha (PIK3CA), cyclin D1 (CCND1), fibroblast growth factor receptor (FGFR), PTEN, ERBB2 (amplification), neurofibromatosis type 1

Table 4. Anticipated assignment rate and expected subprotocol enrollment with screening accrual of 5000 patients based on mutation frequencies and tumor histology in NCI-MATCH interim analysis results in 645 screened patients*

Target (subprotocol)	Expected assignment rate, %	Expected enrollment, No.
PIK3CA mutation (I)	4.0	89
CCND1 amplification (Z1B)	3.6	79
FGFR1/2/3 mutation or amplification or translocation (W)	2.9	65
PTEN expression loss (P)	2.5	55
ERBB2 amplification (Q)	1.7	44
NF1 (S1)	1.9	41
CDK4/6 amplification (Z1C)	1.7	38
TSC1/2 mutation (M)	1.2	28
AKT1 mutation (Y)	1.2	28
NRAS mutation (Z1A)	1.2	28
NF2 mutation (U)	1.1	26
PTEN mutation (N)	1.1	24
MET amplification (C1)	0.9	21
ERBB2 mutation (B)	0.8	20
BRAF V600 (H)	0.8	19
SMO/PTCH1 mutation (T)	0.6	14
MTOR mutation (L)	0.3	7
BRAF non V600 mutation (R)	0.3	8
EGFR T790M or other rare mutation (E)	0.2	4
ALK translocation (F)	0.2	4
cKIT mutation (V)	0.2	3
EGFR activating mutation (A)	—	—
ROS1 translocation (G)	—	—
GNAQ/GNA11 mutation (S2)	—	—

*— = the expected frequency is below 1% or 1 patient as indicated; ALK = anaplastic lymphoma kinase; AKT = V-Akt Murine Thymoma Viral Oncogene Homolog; BRAF = B-Raf proto-oncogene, serine/threonine kinase; CCN = cyclin; CDK4/6 = cyclin-dependent kinase 4 and 6; MLH1 = mutL homolog 1; EGFR = epidermal growth factor receptor; ERBB2 = receptor tyrosine-protein kinase erbB-2; FGFR = Fibroblast Growth Factor Receptor; GNAQ/GNA11 = G protein subunit alpha q/Guanine nucleotide-binding protein subunit alpha-11; KIT = KIT proto-oncogene, receptor tyrosine kinase; MET = Mesenchymal Epithelial Transition, receptor tyrosine kinase; NCI = National Cancer Institute; NF1 = neurofibromatosis type 1; NF2 = neurofibromatosis type 2; NRAS = Rat sarcoma virus GTPase, neuroblastoma; PIK3CA = phosphatidylinositol 3-kinase catalytic subunit; PTEN = Phosphatase and tensin homolog; SMO/PTCH1 = Smoothed/Patched1; ROS = proto-oncogene tyrosine-protein kinase ROS.

(NF1), and cyclin-dependent kinase 4 and 6 (CDK4/6) would each accrue at least 35 patients, and an additional four subprotocols would accrue nearly 30 patients. Eleven subprotocols addressing molecular alterations with a frequency of 1% or less would likely not reach the accrual goal. As a result, the screening accrual goal was increased from 3000 to 5000 and subsequently to approximately 6000 patients.

Changes made to the NCI-MATCH study after the interim analysis are detailed in Table 5.

Biopsy Safety

Grade 3 biopsy-related toxicities were reported in three of 651 (0.5%) patients with data available at interim analysis (one each with abdominal pain and hypertension, and one patient with pneumothorax and cardiac dysrhythmia); no grade 4 or 5 toxicities were reported (Supplementary Table 2, available online).

Table 5. Changes to NCI-MATCH after interim analysis and effect of changes, where known

Design feature	Original protocol	Amended protocol
No. to screen	3000	6000
No. of subprotocols	10	24
Match rate, %	8.7	25.3
Treatment enrollment rate, % (of matched and eligible patients)*	48.5	To be determined
NGS platform throughput	50/mo	100–150/wk
Tumor tissue	Fresh biopsy	Fresh biopsy or archived tissue if obtained in previous 6 mo and patient had had no response to treatment during past 6 mo
NGS success rate, %	87.3	93.9
Turn-around time	Projected median: 14 d Actual median: 36 d	Projected median: 14 d Actual median: 14 d
Education	—	Added support at ECOG-ACRIN and central laboratory to immediately field questions

*Matched and eligible patients possessed an actionable mutation and did not have any exclusionary characteristics (eg, tumor for which the drug was already approved, cooccurring mutations that would cause resistance to the treatment). ECOG-ACRIN = Eastern Cooperative Oncology Group-American College of Radiology Imaging Network; NGS = Next-generation sequencing; NCI = National Cancer Institute.

Discussion

The implementation of NCI-MATCH provides important information to the field of precision oncology. Concerns regarding the ability to accrue for screening were allayed immediately: the rate of patient entry was almost 10-fold that anticipated, reflecting a large unmet patient need and interest in precision medicine in both academic and community centers.

Recently, several efforts to match patients with early-phase trials have reported that only a small minority of patients were able to enroll on relevant clinical studies due largely to lack of trial availability (21–24). NCI-MATCH partially remedied this limitation with the inclusion of subprotocols employing drugs addressing most of the genomic abnormalities that can presently be targeted in cancer and the ability to enroll patients at over 1000 clinical sites. The accrual rate for the initial 10 subprotocols was clearly too low to sustain a genomic trial with a clinically meaningful match rate. Many screened patients were ineligible for drugs in the initial 10 subprotocols because they had histologies for which the initial treatments were FDA approved. In addition, the time patients were required to be off treatment (4–6 weeks) for molecular profiling as well as processing delays due to inadequate laboratory resources likely allowed patient clinical deterioration and contributed to the low enrollment (48.5%).

Several lessons were learned in implementation of the NCI-MATCH study. First, the inclusion of an interim analysis was key to the success of the entire study. It allowed us to understand the demand for inclusion as well as the types of

molecular alterations found in the population of patients to which NCI-MATCH was directed. This information assisted in forecasting which subprotocols would achieve the desired accrual of patients. Of note, when NCI-MATCH resumed accrual after the interim analysis, 24 subprotocols were available and the assignment rate increased from 5.1% to 25.3%, which was considered reasonable given that patients with actionable alterations for which drugs were approved or for which activity in that tumor was already known were excluded. Second, there is great demand for molecular profiling studies, and the volume of patients seeking these types of studies is larger than the number of patients seeking studies where molecular profiling for eligibility is not required. Adequate laboratory resources must be available and reliable. Third, education of clinical sites is critical. Medical personnel and patients need information to understand that profiling and matching takes some time and that patients must be able to be off therapy for at least 4 weeks. In addition, sites need information that generally more tissue is needed for profiling than the amount required for only diagnosis or confirmation of a malignant histology. Fourth, many actionable molecular alterations occur in 3% or less of patients with refractory malignancies. Trials addressing these alterations require access to a great number of clinical sites, and these sites must have as many treatments available as possible. Fifth, implementation in the NCTN and National Community Oncology Research Program, with investigators familiar with new drug administration and access to tens of thousands of patients with all types of malignancies, worked well. Sixth, the collaborative nature of the study, led by NCI and ECOG-ACRIN with participation of representatives from all the NCTN groups, was critical for success (Supplementary Table 1, available online). Furthermore, incorporation of expert input from across the several operational committees as well as from the principal investigators of the subprotocols and from drug developers in the pharmaceutical industry was essential. The trial necessitated a high level of ongoing involvement of all parties as well as project management support for trial development, protocol and amendment maintenance, and new subprotocol development. We implemented uniformity of approach for drug selection and incorporation and gained efficiencies by having all drugs and assays incorporated under an NCI-sponsored Investigational New Drug Application as well as by use of the NCI Central Institutional Review Board.

Success in precision medicine trials depends on the breadth and quality of the genomic assay(s) used for screening, the type of tumors and frequency of molecular alterations identified among registered patients, the number of treatment options available, and the drug target specificity, efficacy, and tolerability of the selected treatments. Addressing rarer molecular alterations remains a challenge. To accrue the Phase II cohorts of alterations in the prevalence range of 1–2%, NCI-MATCH increased the screening goal. Even then, it was clear that molecular subgroups with a prevalence of less than 1% require additional measures to achieve accrual goals. To complete enrollment on “rare variant” subprotocols, NCI-MATCH has now been modified to enroll patients who have an eligible alteration based on sequencing performed for clinical care at a CLIA-accredited laboratory external to the NCI-MATCH trial. This practicality must be considered in future trials addressing the “long tail” of less common, but still targetable, molecular alterations.

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