nature medicine

Perspective

https://doi.org/10.1038/s41591-023-02379-4

The NCI-MATCH trial: lessons for precision oncology

Received: 23 January 2023

Accepted: 28 April 2023

Published online: 15 June 2023

Check for updates

Peter J. O'Dwyer[1,15] ✉, Robert J. Gray[2,15], Keith T. Flaherty[3,15], Alice P. Chen[4,15], Shuli Li[2], Victoria Wang[2], Lisa M. McShane[5], David R. Patton[6], James V. Tricoli[4], P. Mickey Williams[7], A. John Iafrate[3], Jeffrey Sklar[8], Edith P. Mitchell[9], Naoko Takebe[4], David J. Sims[7], Brent Coffey[6], Tony Fu[7], Mark Routbort[10], Larry V. Rubinstein[5], Richard F. Little[4], Carlos L. Arteaga[11], Donna Marinucci[12], Stanley R. Hamilton[13,15], Barbara A. Conley[14,15], Lyndsay N. Harris[14,15] & James H. Doroshow[4,15]

The NCI-MATCH (Molecular Analysis for Therapy Choice) trial (NCT02465060) was launched in 2015 as a genomically driven, signal-seeking precision medicine platform trial—largely for patients with treatment-refractory, malignant solid tumors. Having completed in 2023, it remains one of the largest tumor-agnostic, precision oncology trials undertaken to date. Nearly 6,000 patients underwent screening and molecular testing, with a total of 1,593 patients (inclusive of continued accrual from standard next-generation sequencing) being assigned to one of 38 substudies. Each substudy was a phase 2 trial of a therapy matched to a genomic alteration, with a primary endpoint of objective tumor response by RECIST criteria. In this Perspective, we summarize the outcomes of the initial 27 substudies in NCI-MATCH, which met its signal-seeking objective with 7/27 positive substudies (25.9%). We discuss key aspects of the design and operational conduct of the trial, highlighting important lessons for future precision medicine studies.

It has long been known that certain malignancies are primarily driven by 'driver' mutations and that inhibition of the affected pathways can lead to a substantial antitumor response and survival advantage. A well-established example is chronic myelogenous leukemia, driven by translocation of chromosomes 9 and 22, which results in formation of the BCR–ABL fusion oncogene. The use of tyrosine kinase inhibitors against this driver has reduced the annual mortality by a factor of 10—from 10–20% annually to 1–2% annually[1]. Other notable examples include *EGFR* mutations in a subset of lung cancers and breast cancers driven by overexpression of *ERBB2* (known as *HER2*), to name but a few[2]—leading to the idea of precision oncology, whereby a treatment is targeted to a specific molecular driver.

It has also become clear that some driver mutations can occur across different tumor histologies, but crucially, these can confer

[1]University of Pennsylvania, Philadelphia, PA, USA. [2]Dana-Farber Cancer Institute – ECOG-ACRIN Biostatistics Center, Boston, MA, USA. [3]Massachusetts General Hospital Cancer Center, Boston, MA, USA. [4]Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD, USA. [5]Biometric Research Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD, USA. [6]Center for Biomedical Informatics & Information Technology, National Cancer Institute, Bethesda, MD, USA. [7]Frederick National Laboratory for Cancer Research, Frederick, MD, USA. [8]Yale University, New Haven, CT, USA. [9]Thomas Jefferson University Hospital, Philadelphia, PA, USA. [10]University of Texas MD Anderson Cancer Center, Houston, TX, USA. [11]UT Southwestern Simmons Comprehensive Cancer Center, Dallas, TX, USA. [12]ECOG-ACRIN Cancer Research Group, Philadelphia, PA, USA. [13]City of Hope National Medical Center, Duarte, CA, USA. [14]Cancer Diagnosis Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD, USA. [15]These authors contributed equally: Peter J. O'Dwyer, Robert J. Gray, Keith T. Flaherty, Alice P. Chen, Stanley R. Hamilton, Barbara A. Conley, Lyndsay N. Harris, James H. Doroshow. ✉e-mail: peter.odwyer@pennmedicine.upenn.edu

https://doi.org/10.1038/s41591-023-02379-4

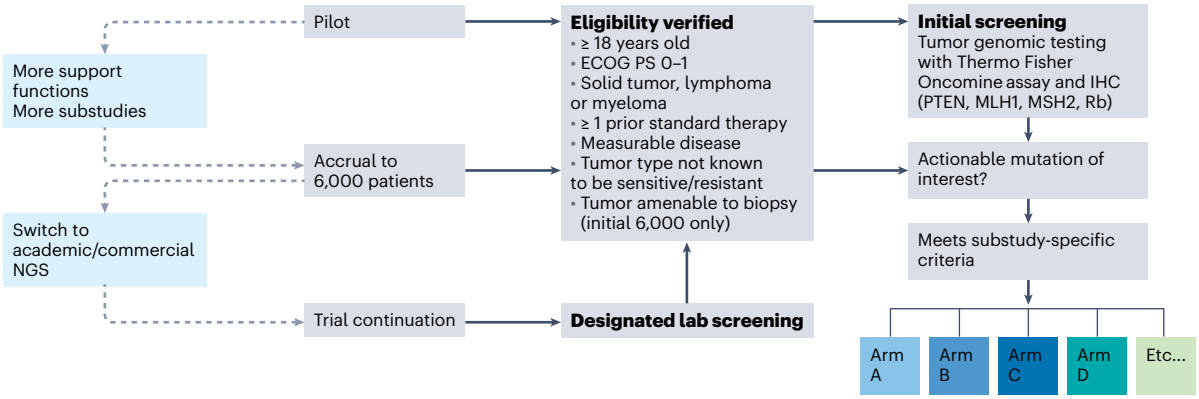

Fig. 1 | NCI-MATCH platform trial design. The trial was implemented in three parts, sequentially: a pilot phase (795 patients) that led to multiple modifications; a screening accrual phase (~6,000 patients); and a continuation phase whereby patients were recruited from a network of academic and commercial laboratories. In the initial 6,000-patient screening period, eligibility was assessed before obtaining a dedicated biopsy sample, while during the continuation period, tumor samples were assayed as part of standard clinical practice, and eligibility was assessed when a candidate mutation was identified. In either case, eligible patients with qualifying tumor molecular aberrations were assigned to a therapeutic substudy, to receive treatment directed to their molecular profile. As a further quality-control measure, for patients tested at designated laboratories, confirmation sequencing was conducted by the NCI-MATCH central laboratories, and only patients whose tumor genomic profile was confirmed in this manner were included for efficacy endpoints. Each substudy was a separate phase 2 trial constituting a drug–genomic driver pair. Patients were assigned to substudies with the assistance of a decision tool (MATCHBox), overseen for appropriateness by a team of medical oncologists, laboratory scientists and bioinformaticists from the trial leadership that reviewed every patient. In each substudy, the initial aim was to accrue 35 patients, assuming 31 would be eligible and start protocol treatment (analyzable); there was provision to increase accrual to 70 in selected arms. The primary endpoint for each substudy was the ORR, defined as the rate of complete or partial response, as assessed by RECIST guidelines[59].

susceptibility to targeted therapies in some tumor sites but not in others. An early example of this complexity was provided by drugs directed to the p.Val600Glu mutation in the *BRAF* gene; while high response rates (40% or more)[3] were observed in patients with melanoma with the aberration, patients with colorectal cancer were almost uniformly resistant[4]. With the development of massively parallel high-throughput genomic sequencing (next-generation sequencing (NGS)) more than a decade ago[5], the broader picture of DNA aberrations across cancers began to emerge, along with myriad potential therapeutic opportunities.

With these considerations in mind, the ECOG-ACRIN Cancer Research Group collaborated with the National Cancer Institute (NCI) to design a trial that would systematically evaluate the activity of the many emerging targeted drugs across a range of different cancer diagnoses. Planning began in 2013 and the NCI-MATCH trial launched in 2015—at that time representing the largest tumor-histology-agnostic, genomically driven clinical trial yet undertaken[6,7]. At the time of its planning, numerous studies attested to the variability of results obtained from different NGS platforms[8,9], prompting implementation of a uniform assay (Oncomine, Thermo Fisher) in four credentialed laboratories, to be applied across all samples[10]. Updates to the assay platform were made to keep pace with scientific developments in the field, including designated immunohistochemical biomarkers for patient selection[11], all the while maintaining a consistent platform for the screened population. When the screening reached the target accrual of 6,000 patients in July 2017, the trial was continued using commercial and academic laboratory testing, until it closed in January 2023. In this Perspective, we summarize the key features of the trial design and conduct, as well as some key challenges and how we addressed these along the way. We discuss the outcomes and limitations, and what they mean for patients and clinicians. The results provide a perspective on the interpretation of the NCI-MATCH trial, and its implications for the design of successor studies.

Trial design and conduct

The design of NCI-MATCH (Fig. 1) has been outlined in detail[6,7]. Each target molecular aberration had to be supported as a driver of tumor growth, and the paired drug demonstrated to inhibit either the driver itself, or the growth pathway activated by it. Each list of qualifying molecular aberrations for a gene was defined through database searches for new experimental or clinical data and was updated regularly as the trial proceeded.

Pilot phase of trial initiation

The NCI-MATCH trial incorporated an initial pilot phase of accrual to assess the distribution of genomic aberrations (given limited sequencing data at the time for metastatic cancers), and to evaluate the performance of all elements needed to provide therapeutic options to patients across a wide geographic area. In the initial 3 months, the trial had ten treatment arms, and the central network comprising four laboratories—harmonized to run assays on an identical platform—was responsible for all the sequencing[6]. Unanticipated enthusiasm in the research community for this trial revealed a number of practical needs—including higher tissue processing and sequencing throughput to enable acceptable turnaround times, and a support desk and broad educational program for clinical providers. The pilot also revealed the need for a substantially higher total screening accrual, since estimates of prevalence based on The Cancer Genome Atlas data (from less advanced cancers) were incorrect by a factor of two or more, and also revealed the need for a greater number of treatment arms to provide options for patients with less-prevalent actionable mutations or alterations. Similar needs were identified in the earlier SHIVA trial[12], conducted with a small number of treatment arms across multiple institutions in France—indicating the importance of large numbers of therapeutic options in future precision oncology trials.

As had been hoped at the outset, most of the accrued patients were not from the four most common tumor types (breast, lung, colon and prostate cancers); over 60% were from less common or rare histological types (Table 1)[6]. Furthermore, new biopsy specimens of metastatic disease were successfully acquired[7], with the aim of capturing new genomic changes that may have occurred since earlier collection of primary tumor tissue[6].

Screening of 6,000 patients with a dedicated assay

Following the pilot phase, 24 available treatment arms (subsequently expanded to 38 in total) were approved, and a revised goal for 6,000

https://doi.org/10.1038/s41591-023-02379-4

Table 1 | Total accrual by disease to NCI-MATCH

Cancer type	Screening cohort *N*=6,390	Outside assay *N*=762
Colorectal	963 (15.1%)	76 (10%)
Breast	764 (12%)	85 (11.2%)
Ovarian	610 (9.5%)	38 (5.0%)
Lung (non-small cell)	485 (7.6%)	53 (7.0%)
Pancreas	413 (6.5%)	25 (3.3%)
Uterine	402 (6.3%)	70 (9.2%)
Liver and hepatobiliary	290 (4.5%)	39 (5.1%)
Sarcoma	288 (4.5%)	29 (3.8%)
Head and neck	239 (3.7%)	34 (4.5%)
Neuroendocrine	214 (3.3%)	11 (1.4%)
Gastroesophageal	211 (3.3%)	34 (4.5%)
Prostate	157 (2.5%)	33 (4.3%)
Bladder/urothelial	108 (1.7%)	17 (2.2%)
Cervical	103 (1.6%)	9 (1.2%)
Central nervous system	103 (1.6%)	106 (13.9%)
Lung (small cell)	90 (1.4%)	4 (0.5%)
Melanoma	85 (1.3%)	14 (1.8%)
Kidney	83 (1.3%)	12 (1.6%)
Lymphoma	55 (0.9%)	1 (0.1%)
Mesothelioma	55 (0.9%)	2 (0.3%)
Anal	52 (0.8%)	6 (0.8%)
Myeloma	1 (<0.1%)	1 (0.1%)
Other	619 (9.7%)	63 (8.3%)

patients to be screened was set. With the increase in available therapies, the treatment assignment rate increased from ~8% to 17.8%, despite each arm of the trial excluding patients if it was already known (based on phase 2 or phase 3 data) that the drug was either active or inactive in that patient's cancer type[7]. The proportion of patients with an actionable mutation (one for which any targeted therapy was available within NCI-MATCH or outside the trial) was over twice this rate, at 37.6%—indicating that nearly two of five patients with advanced cancer may have a candidate treatment revealed by NGS of their tumor. Given the continuing development of targeted drugs and therapeutic protocols, this finding in an unselected population may be a starting point for future trials designed to investigate and establish the efficacy of molecularly targeted therapies and their contribution to patient outcome. The proportion of screened patients who were actually registered for treatment was 12.4%, representing 70% of all patients assigned to a treatment arm; interim disease progression and consent withdrawal are believed to be the major contributors to the fractional registration.

Trial continuation beyond central molecular screening

At the conclusion of the biopsy screening portion of the trial in July 2017 (2 years ahead of schedule), 5,961 patients had been enrolled for molecular profiling, and 11 treatment substudies had completed full accrual. By that time, the sequencing landscape had also changed, and greater methodological consistency resulted in high reproducibility of genomic findings across a variety of sequencing platforms[9]. Also, there was a desire to speed up the identification of patients with rare targetable tumor mutations. To this end, NCI-MATCH expanded its reach by engaging a network of academic and commercial laboratories (termed the NCI-MATCH Designated Laboratory Network), which performed NGS assays as routine care at sites participating in the trial. After a careful vetting process, a total of 30 laboratories (12 commercial and 18 academic) were approved to identify patients for this next phase of the trial, resulting in the treatment of an additional 512 patients. In addition, evidence accumulating external to the trial did not show a major difference between molecular abnormalities found at initial diagnosis and those found in metastatic disease[2]. Accordingly, the trial was continued using the archived specimens that are usually analyzed in genomic laboratories, without a requirement for a new biopsy. This approach has now been implemented for all current NCI-sponsored solid tumor precision medicine trials.

Outcomes and evaluation of NCI-MATCH

Was the trial feasible?

Feasibility was a concern at the outset of the trial. Thus, the statistical plan included monitoring for insufficient accrual and lack of activity among the arms, as well as stopping rules built into the individual substudies. Concerns about accrual were swept away promptly: registration of 6,000 patients in just 15 months was unmatched in the history of ECOG-ACRIN therapeutic studies. Several other genomically targeted therapy studies conducted in the same time frame also support feasibility. One example is the SHIVA trial, conducted in France, with ten treatment arms[12]. Although there were limitations in terms of the availability of therapies in the SHIVA trial, it accrued 741 patients in 21 months. Another trial in France that required re-biopsy (MOSCATO-01) accrued 1,035 patients over 51 months[13]. Hyman et al. reported on a study of neratinib in 141 patients with a variety of cancers whose tumors harbored mutations in *ERRB2* and *ERRB3* (ref. 14). A large trial of genomically defined maintenance therapy in colorectal cancer (MODUL) has been completed with a total accrual of 824 patients[15]. The VIKTORY trial in Korea accrued 772 patients with gastric cancer in a period of 52 months[16]. These and other trials attest to the ability of the oncology community, researchers and patients together, to develop and implement precision oncology trials. Response data are now available for a substantial proportion (27/38) of the NCI-MATCH treatment arms (discussed below), and 8 arms have been closed based on very low prevalence of the targeted aberration.

Did NCI-MATCH achieve its signal-seeking goal?

The goal of NCI-MATCH was to understand the activity of molecularly targeted therapy applied to cancer gene-defined subsets across different tumor histologies, and to document response—regardless of tumor histological type. The purpose was signal seeking: a specific target number of positive phase 2 studies was not defined, nor was it attempted to define a concept of 'tumor-agnostic activity' in which an agent could be defined as broadly active in cancers with the targeted molecular alteration. Sample size and power calculations stipulated that, for a substudy with 31 analyzable patients, five or more responses (partial or complete) would be required, that is, an objective response rate (ORR) ≥ 5/31 (16%). Given the admixture of multiple tumor types to be accrued in each arm, this ORR was considered indicative of activity across tumor types and worthy of further investigation in a tumor-type-agnostic fashion.

A summary of the outcomes of the 27 substudies reported to date is shown in Table 2. Seven of the 27 arms (25.9%) met the prespecified criterion for positivity. Other arms had lower response rates, some of which may support future development with combinations, or with single agents in specific tumor types. In fact, at least one response was observed in 22/27 (81.5%) of the substudies. Across all the treatment arms reported to date, the overall response rate among evaluable patients was 79/765 (10.3%). In terms of breadth of activity, the combination of dabrafenib plus trametinib in *BRAF* V600-mutant tumors identified activity across a broad range of malignancies[17]. These results contributed to a tumor-type-agnostic accelerated approval for the combination of dabrafenib plus trametinib in patients with *BRAF* V600-mutant tumors. This US Food and Drug Administration

https://doi.org/10.1038/s41591-023-02379-4

Table 2 | Outcomes of the initial 27 substudies (of 38 total) in NCI-MATCH

Arm	Molecular aberration	Treatment	*N* enrolled	*N* evaluable†	Number of responses (%)	6-month PFS	Ref.	Met endpoint?[a]
A	EGFR-activating mutations	Afatinib	19	14	1 (7.1%)	8.9%	40	No
B	HER2-activating mutations	Afatinib	40	37	1 (2.7%)	12.0%	41	No
F	**ALK fusions**	**Crizotinib**	**5**	**4**	**2 (50.0%)**	**25%**	42	**Yes**
G	ROS1 fusions	Crizotinib	4	4	1 (25.0%)	50%	42	No
H	**p.Val600Glu or p.Val600Lys mutations**	**Dabrafenib/ trametinib**	**35**	**29**	**11 (37.9%)**	**68.4%**	17	**Yes**
I	*PIK3CA* mutation without *RAS* mutation or PTEN loss	Taselisib	70	61	0.0%	19.9%	43	No
J	*HER2* amplification	Trastuzumab/pertuzumab	35	25	3 (12%)	25.3%	44	No
K2	**FGFR mutation/fusion**	**Erdafitinib**	**35**	**21**	**3 (14.3%)**	**36.8%**	45	**Yes**
M	*TSC1* or *TSC2* mutations	TAK-228	49	34	5 (14.7%)	28.7%	46	No
N	PTEN aberration, with positive IHC expression	GSK2636771	24	22	0.0%	4.8%	47	No
P	PTEN loss by IHC	GSK2636771	35	32	0.0%	3.3%	47	No
Q	*HER2* amplification	Ado-trastuzumab emtansine	38	36	2 (5.6%)	23.6%	48	No
R	*BRAF* fusions/non-V600 mutations	Trametinib	35	32	1 (3.0%)	17%	49	No
S1	*NF1* mutation	Trametinib	50	46	2 (4.3%)	20.5%	50	No
S2	*GNAQ* or *GNA11* mutation	Trametinib	4	4	1 (25%)	50%	50	No
T	*SMO* or *PTCH1* mutations	Vismodegib	34	22	2 (9.1%)	22.4%	51	No
U	*NF2* mutation	Defactinib	35	30	1 (3.3%)	22.8%	52	No
V	C-kit mutations	Sunitinib	10	8	2 (25%)	25%	53	No
W	FGFR pathway aberrations	AZD4547	52	48	4 (8.3%)	15.0%	54	No
Y	***AKT* mutations**	**Capivasertib**	**35**	**35**	**10 (28.6%)**	**50.0%**	19	**Yes**
Z1A	*NRAS* mutations	Binimetinib	53	47	1 (2.1%)	29.2%	55	No
Z1B	*CCND1/2/3* amp and Rb positive	Palbociclib	40	32	0.0%	16.0%	56	No
Z1D	**dMMR status**	**Nivolumab**	**47**	**42**	**15 (35.7%)**	**51.3%**	18	**Yes**
Z1F	**PIK3CA mutation**	**Copanlisib**	**35**	**25**	**4 (16.0%)**	**38%**	21	**Yes**
Z1H	*PTEN* mutation without PTEN protein loss	Copanlisib	35	23	1 (4.3%)	14.3%	57	No
Z1K	***AKT* mutation**	**Ipatasertib**	**35**	**26**	**6 (23.1%)**	**52.4%**	20	**Yes**
Z1L	*BRAF* fusions or non-p.Val600Glu, non-p.Val600Lys *BRAF* mutations	Ulixertinib	35	26	0.0%	5%	58	No

†Eligible, treated and variant confirmed by central laboratory testing. [a]A substudy with 31 or more analyzable patients was to be called positive if the null hypothesis of ORR ≤ 5% could be rejected at the one-sided type I error rate of 1.8%; if there were fewer than 31 analyzable patients, a type I error of 5.0% was used. This requires five or more responses (partial or complete) for a substudy with 31 analyzable patients, that is, ORR > 5/31 (16%). IHC, immunohistochemistry; PFS, progression-free survival.

(FDA) approval provides strong support for the impact of genomically driven trials for patients, especially those with less common diseases. It should be noted that despite the modest impact of early inhibitors, signals were also obtained in select genotypes with PI3K–PTEN–AKT pathway aberrations. The AKT inhibitors capivasertib and ipatasertib had almost identical response rates in *AKT* E17-mutated cancers, a mutually validating result[19,20]. Copanlisib in *PIK3CA*-mutated tumors also provided a signal of activity, with a response rate of 16%, and 38% of patients were free of progression at 6 months[21]. These results also provide additional impetus for the study of mutation-specific agents directed to these targets.

Therefore, even in a heavily pretreated population, the goal of identifying signals was met, although the majority of the arms did not meet the activity threshold, and none of the positive arms had response rates in the range of highly active targeted single agents, for example, imatinib in gastrointestinal stromal tumor[22]. Consequently, NCI-MATCH led to additional questions about what factors influence response to a given agent when the targeted mutation is present. Illuminating such complexity may be possible upon completion of additional sequencing (whole-exome sequencing, RNA sequencing and others) and circulating tumor DNA (ctDNA) analyses of pretreatment and progression samples—and may encourage combination studies at earlier stages of patients' treatment courses.

Limitations of NCI-MATCH

Design limitations. This trial does not provide an evaluation of the efficacy of using genomics to target molecular abnormalities in patients with metastatic cancer. The 'match rate' refers only to patients who had the index molecular variant when an appropriate substudy was available. At the time of screening, the appropriate substudy for any given patient might not have been available, and thus the patient could not be accrued. In regard to response, NCI-MATCH was a signal-seeking

BOX 1

Key lessons from NCI-MATCH to guide future precision medicine trials

1. Proactive outreach is needed to ensure optimal patient (and provider) diversity.
2. Rare tumors are an area of unmet need that can be met (at least in part) with genomic trials; but novel trial designs and regulatory approaches are needed.
3. A clinically relevant definition of 'driver mutation' will be helped by rigorous criteria for evidence to support the matching of therapy to mutation, enabling greater therapeutic activity.
4. Circumvention of resistance mechanisms will be helped by intervention earlier in the disease course, and progress will be accelerated by combination approaches involving targeted therapies and immunotherapies.
5. Trial design should encompass as many therapeutic options for as many molecular aberrations as possible, so as to have an impact commensurate with the collective effort required.

trial, with response assessed in a tumor-agnostic way—and as such the analysis could not provide response rates for specific tumor types as, by design, it was not powered to accrue enough patients to do so.

Operational limitations. Even with a central institutional review board, the time it took to open a substudy was long, sometimes approaching a year. Various scenarios contributed, including issues with drug supply or change in formulation, awaiting phase I results, protocol preparation, education of site staff and individual site review, and stress on the clinical and ethical protocol evaluation system. In some cases, not all patients accrued could be evaluated for the primary endpoint, due to lack of tissue availability for confirmatory sequencing by the NCI-MATCH assay. In future, this confirmatory step should not be necessary, given the high reproducibility of the assay.

Diversity of accrual. The racial/ethnic composition of the patients accrued to NCI-MATCH did not mirror distributions within the US population at large. Among all registered patients, 9.3% were Black people, 5.6% were Hispanic and 3.9% were Asian. All these frequencies appear to be lower than catchment area population representation, although a formal analysis was not conducted and comparator data are difficult to collect, due to the large number of sites ($n = 367$) that accrued at least one patient. Proportions of different groups were almost identical in both the initial screening phase and subsequent periods of accrual, consistent with similar profiles of participating oncologists. In the absence of detailed information on social determinants of health for participants in the NCI-MATCH accrual, there remain questions as to how geographically and socioeconomically representative the trial population is. More detailed reporting of social determinants of health, together with proactive outreach to underserved populations, is needed to provide access for a diverse population to precision oncology trials.

Implications of the NCI-MATCH trial

This trial was established during a period of controversy over the value of genomically driven clinical trials, whether or not such trials could be accomplished by the National Clinical Trials Network, and whether any patient benefit would be realized. The results have highlighted specific topics to be addressed, based upon the lessons learned (Box 1). These fall into four main categories: the definition of rare tumors, the relative contributions of tissue of origin and molecular subtype to outcomes, next steps to design genomic cancer clinical trials, and understanding of co-mutations and the tumor microenvironment.

Defining rare tumors

Rare tumors have typically been specified by histology or tissue of origin, and are conventionally considered those with a prevalence of less than 15 per 100,000 population[23]. By this definition, all but 11 tumor types are classified as rare. Pediatric tumors also need to be considered by these criteria, and the initiation of the Pediatric-MATCH clinical trial (NCT03155620) recognizes this need[24]; a retrospective review of all screened cases applied the World Health Organization International Classification of Diseases for Oncology (ICD-O-3), and this provided greater diagnostic specificity compared to the MedDRA disease coding captured during the study (unpublished). In addition, the advent of broadly available sequencing suggests two further rare tumor groups: unusual genomic profiles within a particular tumor type, and unusual genomic drivers across tumor types. Certain genomic aberrations are closely associated with some rare tumor subtypes, but may also be found sporadically in other tumor types, for example, neurotrophic tyrosine receptor kinase fusions[25] (neurotrophic tyrosine receptor kinase inhibitors have received disease-agnostic approval).

A question of therapeutic interest has long been whether the histological tumor type or the genomic driver should be the more important consideration in choosing a treatment. Regardless of how a 'rare tumor' is defined, it is evident that a precision medicine approach is required for the 25% of adults who have a tumor type that is below a prevalence of 15/100,000, and for additional genomic and histopathological subsets of cancer. We emphasize the precision approach since it has both immediate and long-term implications for cancer diagnosis and treatment: immediate, in that many therapies are already approved, or are in development for specific genomic aberrations. These rare tumors provide a proof of principle: that outcomes are better when a vulnerability can be identified, even when we may not have all the tools at our disposal to effect a cure. But as importantly, the classification of these rare tumors opens for patients the possibility of clinical research options that would otherwise not be available, permits the design of a series of trials to build upon positive results, and may facilitate regulatory decision-making. Further, the NCI-MATCH trial shows that such treatment can be delivered in community and academic settings.

The finding that 38% of the accrual to the NCI-MATCH trial was in rare or uncommon cancers (defined histologically) raises issues relevant to treatment of these patients[26]. Overall, the frequency of 'actionable' genomic aberrations is similar among rare versus common cancers, as is the degree of benefit from interventions[27]. Further, the use of more extensive analyses such as whole-genome sequencing may identify actionable aberrations in as many as 62% of a large sample (including rare and common cancers)[28]. Therefore, a strong rationale exists to examine genomic characteristics of all rare tumors, given that they have fewer treatment options to begin with.

How are the successes in this setting to be made widely available (or commercialized, which generally amounts to the same thing) to patients with rare tumors? The FDA Oncology Center of Excellence has provided extensive guidance to address this issue, with a recent focus on the opportunities to bring real-world evidence to bear on trials in rare tumors (https://www.fda.gov/about-fda/oncology-center-excellence/oce-rare-cancers-program). In genomic subgroups in which a response signal has been observed, how will it be feasible to develop studies to render this signal more effective, if not curative? Large-scale deep-sequencing analyses of samples from patients treated within substudies of NCI-MATCH are ongoing, and will provide hypothesis-generating approaches regarding molecular characteristics that influence response[29]. In future trials, such comprehensive

analysis methods (that are available at major centers) would need to be incorporated into the clinical trial procedures within a practical time frame, using tissues or other samples that can be acquired, transported, stored and analyzed uniformly.

Impact of tissue of origin versus molecular subtype in response

Although not the primary goal of NCI-MATCH, the trial has made several contributions to this dialogue in precision medicine. One of the most revealing and impactful results emerged from the *BRAF* substudy (arm H; Table 2), in which patients harboring a *BRAF* V600E mutation were offered a combination of dabrafenib (a BRAF inhibitor) and trametinib (a MEK inhibitor) as dual inhibition of the MAP kinase signaling pathway. As noted previously, RAF-directed therapy is highly effective in some diseases (such as melanoma)[3] but is almost inactive in colon cancer with a *BRAF* V600 mutation[4]. In NCI-MATCH, tumor types such as these (as well as lung and thyroid cancers), in which the effect of combined therapy was already known, were excluded from the substudy. Patients in the initial 35-patient cohort harbored a broad range of histologies and the response rate (38%) was substantial[17]. These results strongly suggest that response to inhibiting this pathway is indeed disease agnostic. With additional disease-specific sensitivities observed in a parallel Novartis trial[30], the FDA was approached by Novartis and ECOG-ACRIN for a disease-agnostic indication, which was approved under accelerated approval provisions in June 2022.

These findings contrast with those of capivasertib and ipatasertib (arms Y and Z1K, respectively) in *AKT* E17K-mutated cancers, where lower response rates (around 20%) were identified in the substudies for each agent. In both treatment arms, the aberration was identified most frequently in women's cancers, including breast, endometrial, ovarian and cervical cancers. Furthermore, responses were largely confined to these tissue types, suggesting that both tissue of origin and mutation are required for response in these circumstances. Future trials will be needed to further address this issue.

Relevance to genomic cancer trials

Beyond demonstration of feasibility, one must ask how these results inform the development of future studies directed to patients with genomically defined cancers. The characterization of molecular changes in individual cancers has led the field of precision medicine and has greatly changed the outcomes of treatment for specific patients. One need only look at the falling death rates from lung cancer (where EGFR- and ALK-directed therapies have had a clear impact)[31], or the improved outcomes for patients with metastatic melanoma (once it became possible to target mutant *BRAF*)[32], to appreciate that effective molecular medicine has changed standards of care in oncology. It should also be pointed out that the incremental survival benefits observed in patients with metastatic melanoma harboring mutant *BRAF*, translates to higher cure rates when brought forward to the adjuvant treatment setting[33]. In the NCI-MATCH trial, in all but three arms, the intervention tested was a single agent. The limitations of single-agent therapies in this trial echo what has been observed for many years with traditional chemotherapy and anti-HER2 therapy in breast cancer, for example. In this context, the overall response rate of 10.3% observed in NCI-MATCH (across all arms) may be viewed as meaningful for future research in the area. The implications of these results are as much strategic for therapeutics as they are specific to trial design. Sequencing of cancer tissues is needed to identify potential vulnerabilities in the tumor, and this trial provides an impetus to direct treatment to these vulnerabilities as early as possible in a patient's time course. It is recognized that single-agent treatments will have limited effects, and that rational combinations to overcome resistance should be explored early, especially in potentially curative settings.

This was not a trial in which therapy directed to resistant disease could be explored. It does, however, set the stage for future studies of this nature, and a trial called ComboMATCH (NCT05564377), also to be coordinated by ECOG-ACRIN, will investigate combinations of therapies in similar molecular subtypes of cancer[34]. The combinations to be tested in ComboMATCH will require in vivo evidence of efficacy for the combination in well-characterized relevant tumor models and will be restricted to targeted therapies. Given that many of the frequently co-occurring mutations are currently considered undruggable, research on combinations with immune therapies and other modalities should be a high priority.

Co-mutations and the tumor microenvironment

A major finding of the molecular analysis of NCI-MATCH (and other sequencing studies of advanced cancers[27,28]) was that most patients whose tumors had a qualifying mutation also had at least one co-occurring mutation that was known—based on preclinical evidence—to contribute to drug resistance. Some of these have already been outlined[7], and additional sequencing and ctDNA analysis is underway to characterize more completely the tumors of treated patients. Most of these additional mutations (for example, in *TP53*, *KRAS*, *p16* and *MYC*) are currently undruggable, although candidate molecules are in development. Nearly all arms of NCI-MATCH were targeting oncogenic alterations that are known to be truncal. This circumstance facilitated reliance on the Designated Laboratory Network and use of archival tumor specimens as a source for sequencing. However, many of the co-occurring alterations were subclonal and so possibly acquired in response to prior therapy[35]. For trials aiming to overcome resistance mediated by these co-occurring alterations, repeat tumor biopsies or ctDNA analysis of mutation profiles continue to be important considerations.

Alternative approaches to addressing resistance in these subclones should also be explored. Hahn et al. have recently characterized cancer targets as either 'intrinsic' to the cancer itself (such as oncogenes, as well as epigenetic, metabolic, transcriptional or signaling dysregulation, and DNA damage response aberration) or 'extrinsic', involving cellular components of the tumor microenvironment (such as immune cells, cancer-associated fibroblasts, and blood vessels)—all of which contribute to tumor growth and progression, and are therefore plausible targets[36]. The combination of targeted therapies with agents directed at the tumor microenvironment is yielding regimens with markedly enhanced activity. The multi-kinase inhibitor cabozantinib, combined with the anti-programmed death-1 antibody nivolumab in kidney cancer, is a salient recent example[37]—as is vemurafenib (BRAF inhibitor) with rituximab (anti-CD20) in hairy-cell leukemia[38], with many more trials in prospect. Precision cancer studies should include collection of appropriate specimens for research into which molecular or patient characteristics contribute to response or resistance to combined targeted and immunological treatments. A precision medicine trial that would address such combinations directed to genomically defined subsets is a current need with considerable therapeutic potential.

Conclusion

In addition to its impact in clinical research, the NCI-MATCH trial emphasizes the importance of tumor DNA sequencing as part of the standard evaluation of most patients with cancer, given that more than one-third of patients will be shown to have a cancer for which the outcome can be improved with targeted therapy. Since the disease type alone cannot predict the molecular characteristics of individual tumors, implementing such interventions is not currently possible without genomic sequence information.

There are often questions as to the value of routine sequencing; we emphasize that NCI-MATCH was not set up to address this question. Relating the number of responses to the number screened is not meaningful; while some 17% of those screened could be assigned to a treatment arm, there was a total of 38% with driver mutations for whom

a treatment could have been available. Assignment to treatment in NCI-MATCH depended on whether the substudy was open or closed in general, and for the patient's tumor type in particular—as some tumors were more likely to have a given genomic variant, and the numbers of such tumors in a given substudy were restricted to allow a broader recruitment of tumor types, as required by study design. In addition, patients with tumors for which a treatment was known to be effective were not eligible, because the purpose of the trial was to address what was unknown. For all these reasons, while the value of a genomic screening policy is not represented by any proportion of responders to numbers screened in NCI-MATCH, the results clearly support availability of NGS to patients with advanced cancer.

Nevertheless, it is abundantly clear with emerging data that diseases such as melanoma, lung cancer, colon cancer and gynecologic malignancies, as well as some rarer cancers, all now have expanded treatment options resulting from available detailed sequence analyses. Furthermore, the increasing technological capacity of sequencing and other emerging genomic characterization tools to identify evolution of subpopulations of tumor cells over time holds the promise of early approaches to target resistant clones. Although not addressed by NCI-MATCH, germline sequencing of patients with cancer is also receiving considerable attention, and has been implemented in Pediatric-MATCH[24,39].

These results have implications for the critical elements of future platform trial designs: rigorous molecular characterization and objective assignment of patients to treatment arms; tumor sample acquisition to enable retrospective additional sequencing and immune system evaluation to define better who will respond; pathology review of tumor specimens from treated patients as a key quality factor; and sufficient numbers of treatment arms to warrant the efforts both in the cooperative groups that run the trial, and in the community, where the resources for trial activation and management compete with other research priorities. Put another way, to be motivated to open a complex trial, oncologists must have confidence that their patients will benefit through availability of novel therapies that would be otherwise inaccessible.

References

1. Jabbour, E. & Kantarjian, H. Chronic myelogenous leukemia: 2020 update on diagnosis, therapy and monitoring. *Am. J. Hematol.* **95**, 691–709 (2020).
2. Waarts, M. R., Stonestrom, A. J., Park, Y. C. & Levine, R. L. Targeting mutations in cancer. *J. Clin. Invest.* **132**, e154943 (2022).
3. Flaherty, K. T. et al. Inhibition of mutated, activated BRAF in metastatic melanoma. *N. Engl. J. Med.* **363**, 809–819 (2010).
4. Kopetz, S. et al. Phase II pilot study of vemurafenib in patients with metastatic BRAF-mutated colorectal cancer. *J. Clin. Oncol.* **33**, 4032–4038 (2015).
5. Wheeler, D. A. et al. The complete genome of an individual by massively parallel DNA sequencing. *Nature* **452**, 872–876 (2008).
6. Flaherty, K. T. et al. NCI-MATCH Team. The Molecular Analysis for Therapy Choice (NCI-MATCH) trial: lessons for genomic trial design. *J. Natl. Cancer Inst.* **112**, 1021–1029 (2020).
7. Flaherty, K. T. et al. NCI-MATCH team. Molecular landscape and actionable alterations in a genomically guided gancer clinical trial: National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH). *J. Clin. Oncol.* **38**, 3883–3894 (2020).
8. Rehm, H. L. et al. Working Group of the American College of Medical Genetics and Genomics Laboratory Quality Assurance Commitee ACMG clinical laboratory standards for next-generation sequencing. *Genet Med.* **15**, 733–747 (2013).
9. Xuan, J., Yu, Y., Qing, T., Guo, L. & Shi, L. Next-generation sequencing in the clinic: promises and challenges. *Cancer Lett.* **340**, 284–295 (2013).
10. Lih, C. J. et al. Analytical validation of the next-generation sequencing assay for a nationwide signal-finding clinical trial: Molecular Analysis for Therapy Choice Clinical Trial. *J. Mol. Diagn.* **19**, 313–327 (2017).
11. Khoury, J. D. et al. Validation of immunohistochemical assays for integral biomarkers in the NCI-MATCH EAY131 clinical trial. *Clin. Cancer Res.* **24**, 521–531 (2018).
12. Le Tourneau, C. et al. SHIVA investigators. Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial. *Lancet Oncol.* **16**, 1324–1334 (2015).
13. Massard, C. et al. High-throughput genomics and clinical outcome in hard-to-treat advanced cancers: results of the MOSCATO 01 trial. *Cancer Discov.* **7**, 586–595 (2017).
14. Hyman, D. M. et al. HER kinase inhibition in patients with HER2- and HER3-mutant cancers. *Nature* **554**, 189–194 (2018).
15. Schmoll, H. J. et al. MODUL-a multicenter randomized clinical trial of biomarker-driven maintenance therapy following first-line standard induction treatment of metastatic colorectal cancer: an adaptable signal-seeking approach. *J. Cancer Res. Clin. Oncol.* **144**, 1197–1204 (2018).
16. Lee, J. et al. Tumor genomic profiling guides patients with metastatic gastric cancer to targeted treatment: The VIKTORY Umbrella Trial. *Cancer Discov.* **9**, 1388–1405 (2019).
17. Salama, A. K. S. et al. Dabrafenib and trametinib in patients With tumors with *BRAF V600E* mutations: results of the NCI-MATCH trial subprotocol H. *J. Clin. Oncol.* **38**, 3895–3904 (2020).
18. Azad, N. S. et al. Nivolumab is effective in mismatch repair-deficient noncolorectal cancers: results from arm Z1D-A subprotocol of the NCI-MATCH (EAY131) Study. *J. Clin. Oncol.* **38**, 214–222 (2020).
19. Kalinsky, K. M. et al. Effect of capivasertib in patients with an *AKT1* E17K-mutated tumor: NCI-MATCH subprotocol EAY131-Y nonrandomized trial. *JAMA Oncol.* **7**, 271–278 (2020).
20. Kalinsky K. M. et al. Ipatasertib in patients with tumors with *AKT* mutations: results from the NCI-MATCH ECOG-ACRIN trial (EAY131) subprotocol Z1K. Presented at: 34th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics, Barcelona, Spain; Abstract 11 (2021).
21. Damodaran, S. et al. Phase II study of copanlisib in patients with tumors with *PIK3CA* mutations: results from the NCI-MATCH ECOG-ACRIN trial (EAY131) subprotocol Z1F. *J. Clin. Oncol.* **40**, 1552–1561 (2022).
22. Tuveson, D. A. et al. STI571 inactivation of the gastrointestinal stromal tumor c-KIT oncoprotein: biological and clinical implications. *Oncogene* **20**, 5054–5058 (2001).
23. National Cancer Institute. NCI Dictionary of Cancer Terms. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/rare-cancer/
24. Parsons, D. W. et al. NCI-COG Pediatric MATCH Team. Actionable tumor alterations and treatment protocol enrollment of pediatric and young adult patients with refractory cancers in the National Cancer Institute-Children's Oncology Group Pediatric MATCH Trial. *J. Clin. Oncol.* **40**, 2224–2234 (2022).
25. Chen, Y. & Chi, P. Basket trial of TRK inhibitors demonstrates efficacy in TRK fusion-positive cancers. *J. Hematol. Oncol.* **11**, 78 (2018).
26. Gatta, G., RARECAREnet working group. et al. Burden and centralised treatment in Europe of rare tumours: results of RARECAREnet—a population-based study. *Lancet Oncol.* **18**, 1022–1039 (2017).
27. Hoes, L. R. et al. Patients with rare cancers in the Drug Rediscovery Protocol (DRUP) benefit from genomics-guided treatment. *Clin. Cancer Res.* **28**, 1402–1411 (2022).

28. Priestley, P. et al. Pan-cancer whole-genome analyses of metastatic solid tumours. *Nature* **575**, 210–216 (2019).
29. Wheeler, D. A. et al. Molecular features of cancers exhibiting exceptional responses to treatment. *Cancer Cell*. **39**, 38–53 (2021).
30. Adashek J. J. et al. Tissue agnostic activity of BRAF plus MEK inhibitor in *BRAF* V600 mutant tumors. *Mol. Cancer Ther*. https://doi.org/10.1158/1535-7163 (2022).
31. Howlader, N. et al. The effect of advances in lung-cancer treatment on population mortality. *N. Engl. J. Med.* **383**, 640–649 (2020).
32. Kahlon, N. et al. Melanoma treatments and mortality rate trends in the US, 1975 to 2019. *JAMA Netw. Open.* **5**, e2245269 (2022).
33. Long, G. V. et al. Adjuvant dabrafenib plus trametinib in stage III *BRAF*-mutated melanoma. *N. Engl. J. Med.* **377**, 1813–1823 (2017).
34. Meric-Bernstam F, et al. National Cancer Institute Combination Therapy Platform Trial with Molecular Analysis for Therapy Choice (ComboMATCH). *Clin. Cancer Res.* https://doi.org/10.1158/1078-0432.CCR-22-3334 (2023).
35. Dentro, S. C. et al. PCAWG Evolution and Heterogeneity Working Group and the PCAWG Consortium. Characterizing genetic intra-tumor heterogeneity across 2,658 human cancer genomes. *Cell* **184**, 2239–2254 (2021).
36. Hahn, W. C. et al. Cancer Target Discovery and Development Network. An expanded universe of cancer targets. *Cell* **184**, 1142–1155 (2021).
37. Choueiri, T. K. et al.; CheckMate 9ER Investigators. Nivolumab plus cabozantinib versus sunitinib for advanced renal cell carcinoma. *N. Engl. J. Med.* **384**, 829–841 (2021).
38. Tiacci, E. et al. Vemurafenib plus rituximab in refractory or relapsed hairy-cell leukemia. *N. Engl. J. Med.* **384**, 1810–1823 (2021).
39. Mandelker, D. & Zhang, L. The emerging significance of secondary germline testing in cancer genomics. *J. Pathol.* **244**, 610–615 (2018).
40. Reckamp, K. L. et al. Phase II trial of afatinib in patients with EGFR-mutated solid tumors excluding lung cancer: Results from the NCI-MATCH ECOG-ACRIN trial (EAY131) subprotocol A. Presented at: 34th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics, Barcelona, Spain; Abstract 235 (2022).
41. Bedard, P. L. et al. Phase II study of Afatinib in patients with tumors with *HER2*-activating mutations: results from the NCI-MATCH ECOG-ACRIN trial (EAY131) subprotocol EAY131-B. *JCO Precis. Oncol.* **6**, e2200165 (2022).
42. Mansfield, A. S. et al. Crizotinib in patients with tumors harboring *ALK* or *ROS1* rearrangements: results from the NCI-MATCH trial (EAY131) subprotocols F and G. *NPJ Precis. Oncol.* **6**, 13 (2022).
43. Krop, I. E. et al. Phase II study of taselisib in PIK3CA-mutated solid tumors other than breast and squamous lung cancer: results from the NCI-MATCH ECOG-ACRIN rial (EAY131) subprotocol I. *JCO Precis. Oncol.* **6**, e2100424 (2022). PMC8865530.
44. Connolly, R. M. et al. Activity of trastuzumab and pertuzumab in patients with non-breast/gastroesophageal HER2 amplified tumors: results of the NCI-MATCH trial (EAY131) subprotocol. *J. Ann. Oncol.* **31**, S479–S480 (2020).
45. Mita, A. C. et al. Erdafitinib in patients with tumors harboring *FGFR* gene mutations or fusions: results from the NCI-MATCH ECOG-ACRIN trial (EAY131) subprotocol K2. *Mol. Cancer Ther.* 20, Abstract LBA003 (2020).
46. Hays, J. L. et al. Results from the NCI-MATCH ECOG-ACRIN Trial (EAY131)—phase 2 study of MLN0128 (TAK-228) in patients with tumors with *TSC1* or *TSC2* mutations: subprotocol EAY131-M. Presented at: 34th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics; Barcelona, Spain; Abstract 73 (2022)
47. Janku, F. et al. Phase II study of PI3K-beta inhibitor GSK2636771 in patients (pts) with cancers (ca) with *PTEN* mutation/deletion (mut/del) or PTEN protein loss. *Ann Oncol.* 29, Abstract 418PD (2018).
48. Jhaveri, K. et al. Ado-trastuzumab emtansine (T-DM1) in patients with HER2 amplified tumors excluding breast and gastric/gastro-esophageal junction (GEJ) adenocarcinomas: results from the NCI-MATCH Trial (EAY131) sub-protocol Q. *Ann. Oncol.* **30**, 1821–1830 (2019).
49. Johnson, D. B. et al. Trametinib activity in patients with solid tumors and lymphomas harboring *BRAF* non-V600 mutations or fusions: results from NCI-MATCH (EAY131). *Clin. Cancer Res.* **26**, 1812–1819 (2020).
50. Wisinski, K. B. et al. Trametinib in patients with *NF1*-, *GNAQ*- or *GNA11*-mutant tumors: results from the NCI-MATCH ECOG-ACRIN Trial (EAY131) subprotocols S1 and S2. *Ann. Oncol.* 7, e2200421 (2023).
51. Tsao, A. S. et al. Phase II study of vismodegib in patients with *SMO*- or *PTCH1*-mutated tumors: results from NCI-MATCH ECOG-ACRIN trial (EAY131) subprotocol T. *J. Clin. Oncol.* 40, Abstract 3010 (2022).
52. Jackman, D. M. et al. A phase 2 study of defactinib (VS-6063) in patients with NF2 altered tumors: results from NCI-MATCH (EAY131) subprotocol U. *J. Clin. Oncol.* 39, Abstract 3087 (2021).
53. Gien, L. T. et al. Phase II study of Sunitinib in tumors with *c-KIT* mutations: results from the NCI-MATCH ECOG-ACRIN trial (EAY131) subprotocol V. Presented at: 34th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics; Barcelona, Spain; Abstract 238 (2022).
54. Chae, Y. et al. Phase II study of AZD4547 in patients with tumors harboring aberrations in the FGFR pathway: results from the NCI-MATCH trial (EAY131) subprotocol W. *J. Clin. Oncol.* **38**, 2407–2417 (2020).
55. Cleary, J. M. et al. Differential outcomes in codon 12/13 and codon 61 *NRAS*-mutated cancers in the phase 2 NCI-MATCH trial of binimetinib in patients with *NRAS*-mutated tumors. *Clin. Cancer Res.* **27**, 2996–3004 (2021).
56. Clark, A. S. et al. Molecular analysis for therapy choice (NCI-MATCH, EAY131) arm Z1B: phase II trial of palbociclib for CCND1, 2 or 3 amplified tumors. *Cancer Res.* 79, Abstract LB-010 (2020).
57. Janku, F. et al. Phase II study of PI3K inhibitor copanlisib in patients with cancers with deleterious PTEN sequencing results and retained PTEN protein expression: results from the NCI-MATCH Trial (EAY131) subprotocol Z1H. *Ann. Oncol.* **32**, S595–S596 (2021).
58. Subbiah, V. et al. BVD-523FB (Ulixertinib) in patients with tumors with BRAF fusions, or with non-V600E, non-V600K *BRAF* mutations: results from the NCI-MATCH ECOG-ACRIN trial (EAY131) subprotocol EAY131-Z1L. *Proc. Am. Assoc. Cancer Res.* 82, Abstract CT160 (2022).
59. Eisenhauer, E. A. et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur. J. Cancer* **45**, 228–247 (2009).

Author contributions

All authors made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; assisted in drafting the article and/or revising it critically for important intellectual content; and approved the final version to be published.

Competing interests

P.J.O.'D. received research support from Pfizer, Genentech, BMS, AstraZeneca, GSK, Five Prime, FortySeven, Merck, Syndax, BBI, Novartis, Celgene, Incyte, Lilly/Imclone, array, h3biomedicine, Taiho, Minneamrata, pharmacyclics/abbvie and Mirati; and provided

expert testimony for Dai-ichi Sankyo. K.T.F. has served on the board of directors of Loxo Oncology, Clovis Oncology, Strata Oncology, Checkmate Pharmaceuticals, Kinnate Pharmaceuticals and Scorpion Therapeutics; on the scientific advisory boards of PIC Therapeutics, Apricity, Oncoceutics, Fog Pharma, Tvardi, xCures, Monopteros, Vibliome, ALX Oncology, OMRx, Soley Therapeutics and Quanta Therapeutics; as a consultant to Lilly, Novartis, Genentech and Takeda; and received research funding from Novartis and Sanofi. A.J.I. holds stock options in, and has served on the scientific advisory boards of, PAIGE.AI, Kinnate Biopharma, Repare Therapeutics and SequreDx, and has received research support from Invitae. C.A. serves or has served as a scientific advisor to Novartis, Lilly, Merck, AstraZeneca, Daiichi Sankyo, Sanofi, TAIHO Oncology, PUMA Biotechnology, OrigiMed, Arvinas and the Komen Foundation; received grant support from Pfizer, Lilly and Takeda; and holds minor stock options in Provista Diagnostics. The remaining authors report no competing interests.

Additional information

Correspondence should be addressed to Peter J. O'Dwyer.

Peer review information *Nature Medicine* thanks Shumei Kato, Birgit Geoerger and Maud Kamal for their contribution to the peer review of this work. Primary Handling Editor: Karen O'Leary, in collaboration with the *Nature Medicine* team.