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The National Clinical Trials Network: Conducting Successful Clinical Trials of New Therapies for Rare Cancers

Anne F. Schott, MD,

Department of Medicine, Division of Hematology-Oncology, University of Michigan, C349 Med Inn Building, 1500 E. Medical Center Drive, SPC 5848, Ann Arbor, MI 48109-5848

John J. Welch, MD, PhD,

NCI Center for Global Health, Bethesda, Maryland

Claire F. Verschraegen, and

University of Vermont Cancer Center, Division Hematology Oncology

Razelle Kurzrock, MD

Division of Hematology & Oncology, Murray Professor of Medicine, Sr. Deputy Center Director, Clinical Science Director, Center for Personalized Therapy & Clinical Trials Office UC San Diego - Moores, Cancer Center

Abstract

Rare cancers account for 27% of neoplasms diagnosed each year, and 25% of cancer-related deaths in the United States. However, rare cancers show some of the highest response rates to targeted therapies, probably due to identification of oncogenic drivers with little inter-patient variability. Although the low incidence of rare cancers make large scale randomized trials involving single histologies difficult to perform, drugs have been successfully developed in rare cancers utilizing clinical trial designs that combine microscopic anatomies. Such trials are being pursued within the National Clinical Trials Network (NCTN), which possesses unique qualifications to perform widespread molecular screening of tumors for patient enrollment onto therapeutic clinical trials. When larger clinical trials are needed to determine optimum treatment strategies in rare cancers, the NCTN's broad reach in North America and internationally, and ability to partner with both US-based and international research organizations, can make these challenging studies feasible.

Introduction

Among its other objectives, the National Clinical Trials Network (NCTN) is specifically charged with improving the care of patients with rare cancers through clinical trials research.

Corresponding author: Phone: 1-734-936-4991, Fax: 1-734-936-4940, aschott@med.umich.edu.

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In this overview, we discuss the evolving understanding of rare and molecularly-defined cancers, and propose a pathway for study of these diseases.

What is a rare cancer?

Most kinds of cancer are rare; an analysis of the Cancer in North America dataset spanning the years 1995 to 2004 found that 60 of 71 cancer types were infrequent.¹ Only 11 types (prostate, breast, lung/bronchus, colon, uterus, bladder, melanoma, rectum, ovary, non-Hodgkin lymphoma, and kidney/renal pelvis neoplasms) were deemed common among adults in the USA. As a group, rare cancers have a large and growing effect on public health, especially in those who are young, nonwhite, or of Hispanic ethnicity.² The total incidence of all rare tumors combined is substantial, and rates of some have risen steadily over the last several years (for example, adenocarcinoma of the distal esophagus).³

In the United States, the law defines a rare disease as one that affects fewer than 200,000 persons in the nation, i.e., a prevalence of about 64/100,000 persons.⁴ However, this metric poorly reflects the public health burden of cancer, an incident disease.⁵ At a 2007 workshop sponsored by the National Cancer Institute's Epidemiology and Genetics Research Program and the National Institute of Health's Office of Rare Diseases, rare cancers were defined as those cancers for which the incidence rate is less than 15 cases per 100,000 population or fewer than 40,000 new cases per year in the United States.⁶ Although these numbers are relatively small, all rare cancers combined account for 27% of cancers diagnosed each year and 25% of cancer-related deaths in the United States.⁶

With the understanding that cancers are increasingly being defined by specific mutations and characterized by molecular profiles, even common cancers, such as lung or breast cancers, are now subdivided in specific categories that require specific treatments. In effect, molecular classification of cancers leads to a shift where subsets of common cancers now meet the definition of rare cancers. Today, the oncology community is confronted with cancer granularity, which calls for a systemic and critical review of the apparatus of cancer clinical investigation to develop appropriate treatments.

Previous experience in drug development for rare cancers

As a result of legislation aimed at improving drug safety in the USA, the costs associated with drug development increased dramatically. Not surprisingly, pharmaceutical companies responded by concentrating on treatments for common diseases in order to recover drug development costs and generate profits. Consequentially, the plight of patients suffering from rare diseases was largely ignored. These diseases were thus “orphaned.” In order to provide a counterbalance to the regulatory and market forces disincentives that left rare diseases without treatments, a law known as the Orphan Drug Act of 1983⁷ was passed in the United States. It was designed to facilitate the development and commercialization of drugs to treat rare diseases. Orphan drug designation qualified the sponsor for certain attractive benefits from the federal government, including enhanced patent protection and marketing rights.

Molecular characterization: Rare = Homogenous

Rare cancers show some of the highest response rates, likely due to identification of oncogenic drivers with little inter-patient variability. Indeed, it has previously been proposed that when only one or a very small number of aberrant signals lead to a specific type of tumor, it will be both rare and treatable. In contrast, the most common cancers have numerous, diverse, aberrant signals, and they are difficult to impossible to treat with a single agent.⁸ For example, breast and lung cancers, which are common are composed of a multitude of disease subsets, with multiple genomic aberrations. Analysis of the tumors of 57 women with metastatic breast cancer with next generation sequencing (NGS) demonstrated 216 somatic aberrations in 70 different genes, including 131 distinct aberrations. Squamous cell lung cancer, likely initiated by years of exposure to the carcinogenic effects of cigarette smoke, has been shown to have the most underlying variability, with 360 exonic mutations, 165 genomic rearrangements, and 323 segments of copy number alteration per tumor.⁹ In contrast, rare disorders such as Erdheim Chester disease or chronic myelogenous leukemia often have a distinct hallmark, e.g., BRAF mutations¹⁰ or BCR-ABL translocations,¹¹ respectively. This dichotomy may explain the slow, incremental process that has been a hallmark of treatments for cancers such as those originating in the colon, lung and breast. The corollary to these observations is that common cancers are composed of numerous subsets of rare tumors.

Successful FDA approvals

Small subsets within common cancers—Breakthrough therapies have been discovered when common cancers have been stratified into small subsets and assigned molecularly targeted treatment. For example, epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) inhibitors target about 10% and 4% of non-small cell adenocarcinomas, respectively. Specifically, these agents impact tumors with cognate aberrations, that is, EGFR mutations and ALK rearrangements.¹² In the subset of patients with these abnormalities, targeted inhibitors can achieve remarkably high response rates, even in advanced disease. The response rate in patients without the matching aberration is negligible. Importantly, a molecular nosology suggests that most or all tumors will eventually be considered “rare,” implying that treatment paradigms which address uncommon cancers will become increasingly essential.

Small non-randomized subsets of treated patients leading to approval—In a survey of 68 oncology drugs gaining Food and Drug Administration approval from 1973 through 2006 (excluding hormone therapy), 31 gained marketing authorization without a randomized trial.¹³ For these 31 drugs, a median of two clinical trials (range, one to seven) and only 79 patients (range, 40 to 413) were used per approval. Not surprisingly, the vast majority of approvals were for rare neoplasms. Objective response was the most common end point. Median response rate was 33% (range, 11% to 90%). At the time of publication of the survey, 30 drugs were still fully approved.¹⁴ FDA marketing authorization for one drug--the EGFR inhibitor gefitinib--was revoked after a randomized trial showed no survival improvement. However, this trial was performed in unselected patients, and it is now well known that gefitinib is an effective agent when used in patients whose tumors harbor EGFR

activating mutations. The vast majority of these 31 drugs have yielded additional uses recognized with time, and none has been withdrawn due to serious safety signals.

More recently there have been noteworthy examples of accelerated approval in uncommon subsets of common diseases, as well as in rare histologies. For instance, in April 2014, after a phase I study, the FDA granted accelerated approval to the breakthrough drug ceritinib for the treatment of patients with ALK-positive, metastatic non-small cell lung cancer (NSCLC) who progressed on the ALK inhibitor crizotinib.¹⁵ The approval of ceritinib was based on the results of a multicenter, single-arm, open-label clinical trial enrolling a total of 163 patients. The trial showed durable responses of large magnitude with an overall response rate of 44%.

The imatinib story is also remarkable. Imatinib is best known for revolutionizing the outcome of chronic myelogenous leukemia (CML), a rare illness whose hallmark is an aberrantly activated BCR-Abl fusion protein. Imatinib was designed to target this aberrant protein.¹⁶ Because of imatinib (as well as second generation BCR-Abl inhibitors), the median survival of patients with CML has increased from about five to more than twenty years. Imatinib is also effective in and approved for gastrointestinal stromal tumors, an uncommon type of neoplasm that usually carries a *KIT* mutation also targetable by imatinib, and which was notoriously refractory to chemotherapy. Less well known is that imatinib is also approved by the FDA for a host of ultra-rare malignancies: myeloproliferative syndromes with PDGFR rearrangements, mastocytosis without the D816V *KIT* mutation, hypereosinophilic syndrome with *PIPILI-PDGFR alpha*, and dermatofibrosarcoma protuberans (whose hallmark is the *COL1A1 – PDGFB* fusion).¹⁷ The study quoted in the package insert leading to approval was a phase II trial that allowed diverse tumors with cognate abnormalities.^{17,18} Each subset had between 5 and 14 subjects. For some cancers, there were also a handful of additional case reports.

Development of targeted drugs across histologic subtypes

Genomic advances themselves are leading to the reclassification of cancers. Emerging observations indicate that genomic abnormalities do not segregate well simply with organ of cancer origin. As an example, *BRAF* mutations can be found in multiple unrelated malignancies, including but not limited to, melanoma, colorectal tumors, lung and ovarian cancers, as well as hematologic cancers such as hairy cell leukemia, and histiocytosis. Indeed, a small subgroup of almost *all* types of tumors may harbor a *BRAF* mutation.¹⁹ Several drugs that effectively target the *BRAF* mutant protein product have been developed, with vemurafenib and dabrafenib having garnered FDA approval in *BRAF*-mutant melanoma. Importantly, analogous observations are described for many other molecular aberrations; for instance, aberrant HER2 protein expression, gene amplification, and rarely *HER2* mutation characterize a wide spectrum of malignancies.²⁰

A key dilemma, now the subject of vigorous debate amongst oncologists, is whether or not targeted drugs approved for one type of histology should be administered off-label to other histologies harboring the cognate aberration. For instance, should a *BRAF* inhibitor approved for *BRAF*-mutant melanoma be given to a patient with a *BRAF* mutant tumor arising outside the skin? A corollary to this question relates to the specific evidence required

in order to extrapolate predictive data on a biomarker for a given targeted therapy in one cancer to another cancer, as well as what is logistically possible as far as collecting data from clinical studies. Different types of study designs are required to collect these data and may, as in the prior examples cited, lead to specific drug approvals.

Rethinking NCTN Research Strategies for Rare and Molecularly-Defined Cancers

Rare cancer research as a specific charge to the NCTN

The research goals of newly formed National Clinical Trials Network (NCTN) include the study of rare cancers. The NCTN comprises 6 NCI-funded Network Groups that perform cancer clinical trials, reduced from 10 Cooperative Groups in the era ending on March 1, 2014. The Groups boast many years (in some cases, over 5 decades) of experience in clinical investigations, including the study of rare cancers. However, the new NCTN Program Guidelines²¹ released in 2012 emphasized more than ever before the charge of the Network Groups to perform trials in rare cancers. Nineteen individual statements within the NCTN guidelines refer to the study of rare cancers/tumors. For example, on page 22:

The primary goal of NCTN research is to conduct definitive, randomized, late phase clinical treatment trials as part of the NCI's overall clinical research program for adults, young adults and adolescents, and children with cancer. The definitive evaluation of newly developed therapies, including multi-modality treatments, combinations of novel agents, and molecularly-based treatment and advanced imaging approaches, for cancer care will benefit patients and practitioners as well as the entire oncology research community. An equally important focus of the NCTN is an emphasis on trials in special populations (e.g., children, adolescents and young adults, and underserved populations) and rare tumors. This focus allows the NCTN Program to complement, rather than duplicate, research conducted by the private sector.²¹

Table 1 describes some key aspects of performing rare cancer research in the NCTN. Advantages include the NCTN's unparalleled patient access based on the number and diversity of participating sites, including both community and academic settings, and its long and rich experience in clinical trial design and conduct. There are administrative advantages to doing research within the NCTN structure as well. Local activation of an NCTN trial requires much less effort compared with opening an institutional investigator-initiated, or industry-sponsored trial. Members of NCTN groups have access to a menu of active cancer clinical trials, and can select which ones to activate locally, thus eliminating the need for individual trial contracts. Progress has been made in reducing of regulatory burden of maintaining multiple open clinical trials by a mandate that Lead Academic Participating Sites (LAPS) utilize the NCI- funded Central Institutional Review Board (CIRB).

Despite these advantages, rare cancer research in the NCTN is not without significant challenges. The NCTN is currently facing a cap on overall accrual to clinical trials, necessitated by federal funding cuts. In addition, the NCTN's multi-committee, multi-step

trial selection and development process²² does not necessarily prioritize rare cancers. NCTN rare cancer trials that have surpassed these hurdles and are activated have at times languished for poor participation, as the individual sites made decisions not to open a rare cancer study based on their local assessment of the accrual potential to regulatory burden ratio. If it is opened, many sites have institutional rules that automatically close trials that accrue under a threshold rate. Additionally, sites may be concerned their low accrual rates, even when expected, may reflect poorly during programmatic review.

NCI-designated Cancer Centers play an important role in the NCTN, and the latter point has been addressed by the NCI Office of Cancer Centers, which underlined the expectation that these leading academic centers would participate in rare cancer trials, and that Cancer Centers should make exceptions to keep these trials open even in light of low accrual rates. Consistent with this message, the Office indicated that institutions would not be penalized for understandably lower accrual rates for rare cancer clinical trials.²³ As Cancer Centers alter their procedures in response to this guidance, it should increase rare cancer clinical trial activation and increase overall clinical trial accrual, since the centers with the highest enrollments are the ones with many trials open.²⁴

Trial designs for rare cancers

The NCTN Groups are specifically funded by the Cancer Therapy Evaluation Program (CTEP) of the NCI to perform therapeutic drug research with an historical preference for prospective, controlled, randomized single-histology trials. Such trials are difficult to activate, and even more difficult to successfully complete, in rare or molecularly-defined cancers. Many have proposed different approaches for the future. For molecularly-targeted therapies, clinical trials based on cognate genomic aberrations should be the preferred pathway. For multi-modality organ site specific therapies, including surgery, medical therapies, and/or radiation therapy, open-ended single arm trials, or carefully performed prospective registry studies, are most likely to lead to new treatment standards.²⁵

Multiple histological subtypes: “basket trials”—Based on the observation that rare cancers show some of the highest response rates to molecularly targeted therapies, a more efficient way to study rare cancers is through the use of molecularly defined, histology-agnostic trials designated as “bucket” or “basket” studies. Such trials might include patients with a wide variety of histologies as long as they all harbor the cognate anomaly. A current example is a histology-agnostic trial of the BRAF inhibitor vemurafenib that includes diverse types of cancers, providing that they carry the appropriate BRAF mutation.²⁶ While these types of trials are often signal finding, as discussed above, it is of interest, and perhaps a bit unexpected, that the FDA extended the labeled indications of imatinib to include multiple ultra-rare tumors, based on a basket trial that included very small numbers of patients with each of the various histologies.¹⁷

An extension of the basket trial under development in the NCTN is the simultaneous study of multiple drugs/multiple histological subtypes, such as is proposed in the Molecular Analysis for Therapy Choice (NCI-MATCH) project.²⁷ NCI-MATCH will prospectively enroll about three thousand patients who have progressed on at least one line of standard

therapy. Patients will undergo a research-related biopsy for molecular tumor analysis, which will be performed in specified CLIA-certified reference laboratories. At least twenty-five percent of the screened population will consist of patients with histologically rare cancers; genetic variants of common cancers do not count towards this number. The trial aims to develop a longitudinal cohort of patients with multiple histologies who can be matched to one or more embedded single arm drug trials. Each trial will have dual objective response rate and progression free survival primary endpoints.

The main concern of grouping various histologies into one trial, of course, is that certain histologies (rare or otherwise) will have suboptimal responses to matched targeted inhibitors. For instance, the use of BRAF inhibitors has shown excellent responses in *BRAF*-mutant melanoma, thyroid cancer, hairy cell leukemia and histiocytic disease, among others.^{28,29} However, colorectal cancers respond poorly to single agent BRAF inhibitors and are often used as an example that highlights the difficulty of cross- histology extrapolation. On the other hand, emerging data suggests that the *BRAF* mutation is indeed an important target in colorectal cancer, but due to the presence of resistance pathways, BRAF inhibitors alone are inadequate. Combining vemurafenib with the EGFR antibody cetuximab shows evidence of significant activity.³⁰ Although the question of histologic context is not completely answered, it seems likely that driver mutations may be important across diverse histologies, and that optimization of the use of cognate inhibitors may require customized combinations in patients with complex molecular landscapes.

The ultimate goal may be to group biologically similar tumors together, not just on the basis of mutation, but taking into account other factors that cause tumors of different histologies to have similar phenotypes. This process will require active learning in the face of ongoing data collection. Indeed, part of the MATCH trial design includes the active participation of a panel of experts who, when more than one molecular aberration is identified, will attempt to rationally assign patients to a trial possibly more likely to benefit. Although this iterative process may be of concern to some, it is more likely to result in advances in an ever-changing landscape of medical knowledge and drug availability. Confirmatory trials could be designed and performed based on knowledge gained in this process.

Rare subsets of single histological subtypes—Single histology, molecularly-defined trials are more feasible when the malignancy itself is common. The NCTN has recently launched two basket trials targeting rare subtypes within common histologies: the ALCHEMIST and LUNGMAP trials.³¹ In the ALCHEMIST trial (A151216), up to 8000 patients undergoing curative resection of non-small cell adenocarcinoma will be screened for EGFR mutation or ALK-rearrangement. Patients found to have one of these markers will be enrolled in a sub trial in which they will be randomized between an experimental arm consisting of standard therapy plus two years of maintenance therapy of erlotinib (EGFR mutation, sub trial A081105) or crizotinib (ALK rearrangement, sub trial E4512) versus standard therapy. The primary endpoint of both sub trials is overall survival. Tumor specimens obtained both at diagnosis and at time of recurrence will be analyzed by next generation sequencing, providing additional biological insight into these rare subtypes and their evolution during treatment. The LUNGMAP study (S1400) is a true “umbrella” protocol in which patients with second line squamous non-small cell lung cancer will be

screened by a DNA panel plus immunohistochemistry for a variety of DNA and protein aberrations. Patients with a marker of interest will be directed towards a randomized phase II/III sub trial, with objective response and progression free survival assessed at the end of phase II. At the time of launch, LUNGMAP had five sub trials, and more in development. Progression free survival is the primary endpoint of the phase III portion of the study, and overall survival is a secondary endpoint. Given the wide recruitment base of the NCTN, it is estimated that the ALCHEMIST trial will complete recruitment in three to five years. The LUNGMAP study is designed to allow rapid replacement of completed arms, with rapid iteration of drugs failing out at phase II, and completion of the first phase III studies in a three to five year time frame.

Registry Studies—The current reality, for better or for worse, is that patients and physicians have access to commercially available molecular screening tests without participating in a prospective clinical trial. These tests may lead to utilization of existing therapies off-label, and although the response to such treatments may be either overwhelmingly positive or negative, there is currently no systematic way to collect this clinical information, and learn from it. Although the clinical trials database ClinicalTrials.gov lists numerous observational studies dedicated to rare cancers, the rigor of clinical data collection (including collection of information on off-label treatment) through these as a whole is unknown. Many do not list the collection and analysis of genomic cancer data as an objective, and indeed, many were initiated prior to the widespread availability of next generation sequencing for cancer, and the availability of newer targeted agents.

In response to the emphasis placed on the study of rare cancers within the NCTN, the Groups should assume as a part of their mission, the collection and analysis of such data. The NCTN Groups, capitalizing on their access to patients in both community and academic oncology practices, could serve as a basis to accumulate and consolidate knowledge of the natural history, molecular biology, and treatment of rare and molecularly defined cancers. The Children's Oncology Group already sponsors such studies in rare Hodgkin Disease variants,³² in neuroblastoma,³³ and in mixed tumor types,³⁴ but there are currently no examples of rare tumor registries sponsored by the adult NCTN groups. As a start, one, or at most several, rare cancers could be targeted for study. Once a registry was established, it could aggregate (retrospective registry) or in some cases provide (prospective registry) molecular analysis of tumor tissue, and could subsequently link molecular subtypes with treatment outcomes. Patients would consent to participate in the NCTN registry, which would include collection of tissue and tissue-based data, information on treatments received, and survival outcomes. By participating in the registry and contributing tumor tissue, patients may gain the opportunity to participate in one or more of a slate of NCTN trials designed to evaluate specific treatments and symptom control strategies for those with a particular genomic aberration.

Certainly, the NCI-MATCH trial, which will provide molecular screening for 3000 patients (of which 750 must have cancers considered to be “rare”), is a promising first foray into such a prospective genomics registry. However, once the NCI-MATCH experiment is completed, there is no continuation plan. One of the advantages of the MATCH trial is the use of a single screening platform with careful attention to concordance across several

geographically separated labs. The availability of multiple commercial multiplex assays complicates any retrospective registry endeavor, and may necessitate prospective tissue testing on a single platform in order to draw firm conclusions from registry data. There is increasing information that the molecular diagnosis determined on different platforms, or even on one platform but at a different place or time, will not yield concordant results.³⁵ An expanded genomics registry would need to recognize the sensitivity, specificity, and reproducibility (analytic validity) of the included high-throughput multiplexed sequencing technologies.

New Partnerships

In order to speed both the development and dissemination of knowledge for rare and molecularly-defined cancers, the NCTN will need to expand its partnerships to include other NIH components, disease-specific foundations, and patient advocacy groups. Despite the fact that the NCTN Groups have been charged to study rare cancers, they do not receive funding from the Division of Cancer Treatment and Diagnosis for prospective registry studies or for widespread molecular screening outside the context of interventional clinical trials. However, a multitude of other NIH components have interest in rare diseases including the Office of Rare Diseases Research (ORDR), which is under the National Center for Advancing Translational Sciences (NCATS); these NIH components could be approached for collaborative projects. The ORDR in particular hosts programs that could be directly relevant to research in rare cancers, including The Rare Diseases Clinical Research Network (RDCRN), the Global Rare Diseases Patient Registry and Data Repository (GRDR), and the Rare Diseases Human Biospecimens/Biorepositories (RD-HuB).

Two key aspects of the RDCRN are its collaborations with disease-specific foundations, and its partnerships with patient advocacy groups. Such foundations typically have non-profit 501(c)(3) status and offer various activities to patients and enlist rare disease specialists to support their advocacy efforts. Most of them actively fundraise to sustain the efforts. Activities range from educational materials and support systems, research grants, financial assistance for patients, conferences for physicians/scientists and/or for patients, access to clinical research studies and registries, and referral to specialized doctors. Increasing the partnership between well-established rare cancer foundations and the NCTN would create further incentive to study rare and molecularly-defined cancers in a more systematic way.

Patient advocates and patient advocacy groups have long been valuable partners for the NCTN groups, and are active partners in of some of the trials described above, including LUNGMAP. Patient advocacy groups have additional means of communicating with patients and their families, and through these communications they have the potential to speed dissemination of information on emerging cancer therapies, and to positively influence accrual to rare cancer clinical trials.

Developing a global research network for rare cancers

Although single arm, non-randomized trials may be feasible and even lead to drug approval in rare and molecularly defined cancers, as outcomes improve and more treatments become available, there will remain a need for randomized clinical trials to compare the emerging

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available drugs and strategies. At the current time, few rare cancers can be treated by therapies backed by evidence gathered from randomized clinical trials,^{25,36} and to compare therapies for many of these cancers would require trials on an international scale to gain sufficient statistical power. Such international clinical trials would accrue participants faster and offer lower collective administrative costs than would local or regional trials, and collaborating investigators could capitalize on shared infrastructure, centralized resources, and existing networks. Despite their potential advantages, however, financial, logistical, and regulatory challenges make international trials challenging.³⁷

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There is precedent for international collaboration involving the NCTN Groups, particularly for diseases where an unusually large accrual base was needed; for example, to support large adjuvant studies or for noninferiority study designs. Models for the international participation in these trials include enrollment by sites that are members of the NCTN Groups, or enrollment through overseas networks independent of the NCTN Groups, with either the foreign network or NCTN leading the collaboration. However, given the inherent difficulties of conducting studies in rare cancers compounded by the regulatory challenges of working internationally, the only NCTN Group to have significant experience partnering with global networks to perform clinical trials in rare cancers has been the Children's Oncology Group, for example in the EURAMOS consortium.³⁸

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To focus international efforts on rare cancers, the International Rare Cancer Initiative was launched in 2011 by partners including the US National Cancer Institute, Cancer Research UK, the UK National Cancer Research Network and the European Organisation for the Research and Treatment of Cancer, with the French National Cancer Institute joining the partnership in 2013, and the National Cancer Institute of Canada Clinical Trials Group in 2014. The objective of this initiative has been to facilitate the development of definitive treatment clinical trials for cancers that otherwise could not be addressed within individual regional catchments. Specifically, the initiative has focused on cancers with an incidence of less than 3 per 100,000 persons/year, where no other international forum exists to perform a coordinating function, and where treatment is not currently guided by strong evidence.⁵

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The initiative works by identifying common interests to pursue studies in a rare indication and then brings together expert working groups that to date have also included members from clinical trial groups outside the core membership, including Australia, Brazil, Canada, Chile, Japan, Peru, Poland and Russia. When interest exists in enough member networks to make a project viable, the initiative promotes early agreement on design and then shepherds each study from concept evaluation within each network through protocol development, regulatory review and finally the operational steps to launch and run the trial. At each step, the initiative works administratively to perform processes in parallel and constantly learn from and replicate successful practices from previous trials. To date, IRCI trials that have launched have included studies in uterine leiomyosarcoma³⁹, metastatic anal carcinoma⁴⁰, and ocular melanoma.⁴¹ Studies in development include additional gynecological sarcomas,⁴² advanced penile carcinoma,⁴³ small bowel adenocarcinoma⁴⁴, androgen receptor positive salivary carcinoma,⁴⁵ and locally advanced invasive thymoma.

NCTN Groups are not limited to international trial collaborations coming under the banner of this initiative, but may propose to initiate or partner on international trials of interest to their membership. Whether within the initiative or not, all proposed international collaborations involving an NCTN group must undergo both an administrative and scientific review by NCI. This scientific review is typically conducted by a disease-specific NCI Scientific Steering Committee, although studies involving less than 100 subjects may be reviewed by the Cancer Therapy Evaluation Program at NCI. Because the NCTN Groups derive some of their funding from US federal funds, after approval of a study, the NCTN Groups are required to work closely with NCI to assure compliance with applicable federal regulations, including relationships with pharmaceutical companies and partners. This process is often burdensome for both the NCTN Groups and international partners, but with experience is becoming more manageable. Further, improved information technology solutions for clinical trial processes such as remote data capture and querying, randomization and registration, and pharmacovigilance, have facilitated conduct of recent trials.

Conclusions

It is increasingly clear that cancer is being subclassified into smaller genomic subsets and optimization of therapy might require individually tailored drug combinations. Randomized trials for rare tumors and uncommon subsets of common tumors are unlikely to be feasible in the initial steps of single drug or drug combination development. Increasingly, novel designs such as biomarker-driven histology-agnostic trials or genomically driven trials within specific histologies are supplanting older designs that rely on treating unselected groups of patients. For patients with rare or ultra-rare tumors these trials can yield high response rates, and the FDA has shown a willingness to approve biomarker-based breakthrough drugs for cancer, even based on small numbers of patients or Phase I data. To date, rational drug development leading to such approvals has yielded safe agents with remarkable efficacy, some of which are transforming the lives of patients with rare or molecularly-defined cancers.

However, as more drugs and treatments for rare cancers emerge, there will still remain a need for randomized trials or observational studies to compare strategies. The NCTN, in partnership with the National Institutes of Health, rare cancer foundations, patient advocacy groups, and global partners, is uniquely poised to lead research in rare cancers. Continued efforts to reduce barriers to the study and advancement of treatment for rare and molecularly defined cancers are needed.

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Table 1

Aspects of Rare Cancer Research in the NCTN

Advantages	Challenges
Large number of sites increases access to the population	Cap on accrual to NCTN clinical trials necessitated by current budget woes
Diversity of participating sites (research, academic, community) increases generalizability of results	Molecular screening outside of the context of a therapeutic interventional trial is not adequately funded
Rich experience in clinical trial design and conduct within the NCTN	Single arm and observational trials receive lower priority for activation in NCTN
NCTN system obviates need for individual site contracts	Sites may choose to not activate studies that have anticipated low accrual
Central IRB reduces regulatory burden at the individual sites	Not all NCTN trials are eligible for CIRB; not all NCTN centers participate in the CIRB

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