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Transforming the early drug development paradigm at the National Cancer Institute: The formation of NCI's Experimental Therapeutics Clinical Trials Network (ETCTN)

Holly A. Massett¹, Grace Mishkin¹, Jeffrey A. Moscow¹, Amy Gravell², Michael Steketee³, Martha Kruhm¹, Sae H. Han¹, Barbara Barry⁴, Michael Montello¹, James Zwiebel¹, Jeffrey S. Abrams¹, James H. Doroshow¹, S. Percy Ivy¹

¹National Cancer Institute, Bethesda, Maryland ²The Emmes Company, Rockville, Maryland

³Westat, Rockville, Maryland ⁴User-Centered Design Inc., Ashburn, Virginia

Abstract

Early drug development for cancer requires broad collaboration and skilled clinical investigators to enable enrollment of patients whose tumors have defined molecular profiles. To respond to these challenges, the National Cancer Institute (NCI) transformed its 60-year old early phase drug development program in 2014 into the Experimental Therapeutics Clinical Trials Network (ETCTN). The ETCTN is a consolidated, national network of 40+ academic institutions responsible for conducting over 100 early phase clinical trials. It promotes team science coordinated amongst basic, translational and clinical investigators, emphasizing the inclusion of early career trialists. This perspective provides a brief overview of the ETCTN, summarizes its successes and challenges over its first grant funding cycle, and discusses the program's future directions. Measures indicated strong connectivity across the institutions, significant increases in investigator approval of the ETCTN scientific portfolio from Years 1 to 4, and substantial research activity over five years, with 334 letters of intent (LOIs) submitted, 102 trials activated, and 3570 patients accrued. The ETCTN's successful adoption relied heavily on the inclusion of senior investigators who have longstanding interactions with the NCI and a willingness to participate in a team science approach and to mentor early career investigators. Additionally, NCI invested substantial resources in a centralized infrastructure to conduct trials and to support the inclusion of biomarkers in its studies. The ETCTN provides evidence that a collaborative national clinical trial network for early drug development is feasible and can address the demands of precision medicine approaches to oncologic clinical trials.

Keywords

Clinical trials; precision medicine; early drug development; cancer

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Corresponding Author: Holly A. Massett, PhD, 7201 Wisconsin Ave., Suite 2S-603, National Institute on Aging, NIH, Bethesda, MD 20814; Phone: 301-827-7030, massett@mail.nih.gov.

Note: Current address for H. Massett: National Institute on Aging, Bethesda, Maryland

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INTRODUCTION

The National Cancer Institute's (NCI) early therapeutics program has substantially contributed to developing anticancer agents, having filed over 900 Investigational New Drug (IND) applications since the 1950s (1). By the mid-2000s, however, NCI recognized that its predominant drug development model—using single-arm trials answering a single question at a single research site—was inefficient, costly, and poorly positioned for the era of precision medicine, where greater collaboration among institutions is needed to identify and enroll patients with specific molecular profiles (2–5). In March 2014, NCI overhauled its early therapeutics program and launched the Experimental Therapeutics Clinical Trials Network (ETCTN), a highly integrated network emphasizing team science (6). The creation of the ETCTN was part of NCI's larger efforts to modernize and streamline the Institute's clinical trials enterprise, which also included the transformation of NCI's late phase trial cooperative group program into the National Clinical Trials Network (NCTN).

The NCI's vision for the ETCTN was a consolidated, national network of academic cancer centers to facilitate accrual to early phase trials of agents that have been approved by NCI for collaborative development between NCI and industry. These studies address molecularly-defined patient subsets to address clinical and scientific questions not evaluated by the private sector. The ETCTN relies on project teams of basic, translational, and clinical investigators who devise and execute drug development plans, with a major emphasis on including early career investigators alongside senior mentors. NCI provides centralized systems to construct protocols, enroll patients, collect and manage data, report adverse events, and bank tumor tissue, all of which allows multiple sites to function as a network. This perspective provides a brief overview of the ETCTN, summarizes its successes and challenges over its first grant funding cycle, and discusses the program's future directions.

NCI ETCTN MODEL

The ETCTN is housed within NCI's Cancer Therapy Evaluation Program (CTEP) in the Division of Cancer Treatment and Diagnosis (DCTD). It is funded by cooperative agreements with 12 lead academic organizations (LAOs) that are responsible for scientific leadership and accruing patients. Among LAOs, there are 37 Grant Principal Investigators (PIs) who are international leaders in cancer drug development. Each LAO has its own sub-network: The main member (MM; i.e., LAO grantee), other institutions within the MMs' financial and governance structure, and affiliated organizations external to the MM (AOs; N=28; median=2 per LAO; range 1 to 5). LAOs oversee the activation and conduct of NCI's early phase therapeutic trials, comply with required policies and regulations, and activate and support accrual to each other's studies (1). Each LAO has an annual minimum accrual benchmark goal per grant year: 50 patients for phase 1 trials, and 72 for phase 2.

Funding.

Prior to the ETCTN, the early drug development process was funded via UO1 grants for phase 1 trials and NO1 contracts for phase 2 trials. In 2014 with the ETCTN, funding switched to UM1 grants for phase 1 trials but continued with the NO1 contracts until their scheduled end date; at that point phase 2 trials were funded via supplements to the UM1

grants. With the second ETCTN grant cycle, there will be a single UM1 grant for phase 1 and 2 trials, and U24 for pharmacokinetics. The annual approved budget for the ETCTN UM1 cooperative award program, which included funds to complete the legacy phase 1 and phase 2 programs, was approximately \$20M. There were additional contract costs for centralized clinical trial support services.

Clinical Trials.

The ETCTN supports a robust portfolio of trials in partnership with LAOs, provides access to novel agents from industry, acts as an honest broker for drug combination studies (7,8), and assumes regulatory responsibility for the trials as IND holder. NCI supports two pathways for new protocol development within the ETCTN: Project teams and unsolicited trial letters of intent (LOIs). LOIs submitted by early career investigators (< 7 years from oncology training) have a competitive advantage in the prioritization process to decide which studies to perform. Unsolicited LOIs are most typically received by investigators within the ETCTN and less commonly received by those outside the network, though all will be considered for review.

Agents.—CTEP has a broad portfolio of anticancer agents available through agreements between NCI and industry (7). CTEP serves as sponsor for these agents' IND applications. Novel agents are added to the portfolio through NCI's Experimental Therapeutics (NExT) program pipeline (1). NExT provides resources to researchers developing therapies for unmet needs—agents enter NExT at various points in the discovery and development pipeline, and when ready for clinical evaluation, a project team is formed.

Project teams.—A critical expectation of LAOs is to lead and/or participate in multi-disciplinary, multi-institutional scientific project teams to design initial drug development plans for agents approved by the NExT program (3). CTEP and LAOs co-lead teams; members apply via a streamlined project team member application (PTMA) that includes basic, translational, and clinical extramural scientists and early career investigators. Participation requires phone meetings over an average of 6–8 weeks and culminates in a drug development plan to submit to NCI's Investigational Drug Steering Committee (IDSC) for review. After IDSC evaluation, team members submit LOIs to conduct the proposed studies in the plan. LOIs follow CTEP's protocol development processes set forth by NCI's Operational Efficiency Working Group (OEWG) guidelines (9).

Unsolicited LOIs.—Investigators submit unsolicited LOIs to examine novel hypotheses that are supported by preclinical data for any agent in the CTEP portfolio (10). These LOIs cannot compete with studies put forward by a Project Team and may only be submitted after approval of a team's plan. ETCTN investigators submit unsolicited LOIs that follow the OEWG guidelines (9,10) for review by CTEP's Investigational Drug Branch (IDB).

Incorporation of biomarker assays.

Because biomarker assay development is central to the ETCTN's mission, NCI implemented several mechanisms to ensure assays are analytically validated and fit-for-purpose for their

intended use, and that allow for the banking and accession of tissues for future research (see Table 1).

Governance.

Agents under development in the ETCTN are chosen through a peer-review mechanism through NCI's Developmental Therapeutics Program, and then approved by the NCI Division of Cancer Treatment and Diagnosis (DCTD) Senior Advisory Committee, so that agents under development in the ETCTN are selected independently of ETCTN program staff. The drug development activities of the ETCTN are reviewed by the external IDSC who makes recommendations of all initial drug development plans formulated by drug project teams. Both ETCTN grantees and NCI program staff meet with the IDSC quarterly to review proposals from the project teams.

Centralized support.

As part of the larger effort to streamline NCI's clinical trial enterprise described earlier, NCI recognized the need to develop and implement standardized procedures, processes and tools to support centralized clinical trial oversight—from LOI concept review through clinical trial activation, patient accrual, auditing, monitoring, closing a trial and patient safety oversight. To do so, NCI developed a centralized infrastructure to support all ETCTN and NCTN clinical trials; Table 1 provides a summary of the components of this infrastructure.

ETCTN CLINICAL TRIAL PERFORMANCE

Table 2 presents the metrics showing the growth of ETCTN's trial portfolio over its first five grant years (GY). A total of 334 LOIs were submitted (range: 49–80 per year), with the LOI approval rate increasing substantially from 20% in GY1 to 57% by GY5. Of the LOIs, almost half (42%) were led by early career PIs. Since GY1, 19 project teams were initiated; project teams required an average of 7.8 months between approval for Project Team and first LOI submitted for that project team's focus. From GY1 to GY5, 102 ETCTN protocols were activated, with the last three GYs averaging 27 trials activated per year. Additionally, organizations increased the number of trials opened at their sites from an average of <1 trial activated in GY1 to an average of 10 activated in GY5. In five GYs, 3,570 patients were accrued by ETCTN organizations (Figure 1). For GY1 and GY2, most accrual was to legacy trials (i.e., those trials activated in NCI's previous early development program that transitioned into the ETCTN). Accrual lagged for the ETCTN trials through GY2 as few had yet to open at sites due to the lead time required to approve and activate new protocols. As more ETCTN trials opened, accrual increased substantially with ETCTN trials accounting for the majority of accruals by GY3 (vs. legacy trials) and 97% of all accruals by GY5. With respect to productivity of the ETCTN network, over 80 agents have an active CTEP agreement and at least 100 published manuscripts related to ETCTN activities by the end of its first grant cycle. More information on the agents can be found at: https://ctep.cancer.gov/industryCollaborations2/agreements_agents_table.htm.

INVESTIGATOR FEEDBACK

The ETCTN program differed substantially from the predecessor program; therefore, it was important to continually seek input from ETCTN investigators regarding their satisfaction with the ETCTN and identify obstacles to opening and accruing to trials across the network. Two methods were employed: 1) an online satisfaction survey fielded annually during the first three grant years (May: 2015–2017); and 2) 60-minute phone interviews conducted with grant PIs in January 2017 (N=35; of 37) midway through the first grant funding cycle.

Survey.

We assessed the PIs' satisfaction with the ETCTN portfolio using an annual online survey. Invitations were emailed to all PIs who had actively engaged in the ETCTN over the grant year(s). The survey included 13 core questions and took approximately 15 minutes to complete. The survey was considered exempt by the NIH's Office of Human Subjects Research, and responses were confidential with identities unknown to NCI. Statistical testing used SAS (v. 9.4), and we report p-values with a two-sample t-test on mean differences ($p < .05$ was deemed significant).

Across all three years, we achieved high completion rates: Year 1, 81.4% (105 completed of 129); Year 2, 98.7% (152 completed of 154); and Year 3, 92.4% (171 completed of 185). Using a five-point Likert scale (1=not at all satisfied; 5=very satisfied), we found statistically significant increases from Yr1 to Yr3 in the PIs' mean satisfaction with: The number of trials in the ETCTN portfolio (Yr1: 2.36; Yr3: 3.16, $p < 0.01$); number of trials available to open at each respective site (Yr1: 2.51; Yr3: 3.11, $p < 0.01$); representation of therapeutic classes (Yr1: 2.74; Yr3: 3.20, $p < 0.01$); balance of scientific areas (Yr1: 2.94; Yr3: 3.28, $p < 0.01$); and, integration of preclinical findings (Yr1: 3.33; Yr3: 3.59, $p = 0.03$). Similarly, there were statistically significant increases from Year 1 to Year 3 in the PIs' mean level of agreement (1=strongly disagree; 5=strongly agree), with the following statements: "Enough ETCTN trials activated to meet center's accrual goals" (Yr1: 2.23; Yr3: 2.52, $p = 0.05$) and "ETCTN opens up careers opportunities for junior investigators at our site" (Yr1: 3.49; Yr3: 3.78, $p = 0.05$).

In-depth phone interviews.

Interviews with grant PIs solicited PIs' greatest challenges in opening and accruing to ETCTN trials and recommendations that might improve network performance. Interviews revealed five critical challenges: 1) PIs wanted greater incentives to lead new protocols and open other investigators' trials; 2) PIs needed more information and sooner about the ETCTN trial portfolio to plan their own center's trial portfolio and inform disease teams; 3) PIs saw the unsolicited LOI review process as unpredictable and frustrating, requiring time-consuming decisions over minor details; 4) PIs were frustrated with NCI's Central Institutional Review Board (CIRB) for the ETCTN (12), believing too many changes were asked of them and comments appeared to be outside the CIRB's purview; and, 5) PIs wanted NCI to shorten and streamline the OEWG timeline to approve LOIs and activate protocols sooner.

Following interviews, NCI implemented several changes over six months: a) provided additional incentives to grantees such as credits toward an LAO's accrual quota for activating new studies and for opening other LAOs' studies, and authorship potential to PIs who signed up as a trial champion at their site; b) developed communication tools to increase PIs' awareness of the ETCTN portfolio (e.g., CIRB-approved handouts for patients, monthly PI email newsletters providing trial updates by disease, interactive lists of ETCTN active trials); c) created a standardized decision form for LOI disapprovals; d) implemented a contract mechanism to author all ETCTN protocols for PIs with an approved LOI to ensure high-quality documents in a shorter timeframe; and e) reviewed the OEWG processes to address redundant steps and reduce the number of revisions asked of the PI.

COLLABORATION AND CONNECTIVITY

A major ETCTN goal was to evolve a well-connected network among its LAOs and investigators to support NCI's early drug development research portfolio. Two social network analyses were conducted that show ETCTN investigators were highly connected professionally from the onset, and became a well-connected network over time with regard to accruing to each organization's active trials.

Professional Connectivity.

To assess professional connectivity, a question was added to the annual online survey described above for GY1 and GY2. Investigators were provided a list of all ETCTN organizations and asked to mark those institutions where they had direct collaborations with other early phase cancer researchers over the past year (e.g., co-PI, publication, conferences), and to quantify the number of people they collaborated with at each organization and the frequency of their collaborations. NodeXL (12). was used to analyze respondents' inter-organization collaborations over the program's first two years.

Network density (i.e., proportion of collaborations among all potential collaborations) indicated a high degree of professional collaboration from the onset: For GY1, 91% of all possible collaborations amongst organizations was detected, increasing to 97% for GY2, meaning nearly every organization was connected. Network centralization is the extent to which organizations are connected to multiple organizations—lower percentages signify multiple collaborations that are well distributed: Centralization for both years was very low (GY1 at 11% and GY2 at 3.6%).

Accrual Connectivity.

To assess accrual connectivity, we analyzed the degree to which organizations accrued to each others trials for ETCTN's first four years. The annual number of active ETCTN trials (omitting legacy trialsⁱ) was: 4 trials (G1), 18 (GY2), 33 (GY3), and 60 (GY4). The total number of accruals over time to each others' trials was: 36 total accruals in GY1, 183 (GY2), 375 (GY3), and 676 (GY4). Figure 2 is a network visualization of the accrual

ⁱLegacy trials were those trials that LAO sites already had activated under the former early phase drug development program via the former U01 grant mechanism.

network for each year with connections weighted by the number of accruals associated with them, demonstrating substantial growth of shared accrual across four years.

CONCLUSIONS

Within its first five years, the ETCTN has become a highly collaborative network, activating over 100 trials with the majority formulated via the project team process. Most of these studies are led by early stage investigators, supported by senior mentors. Social network metrics indicate the network is aligned for its scientific goals and for patient accrual to trials. Satisfaction measures indicate that network investigators increasingly approve of the ETCTN's scientific portfolio and key organizational challenges have been addressed. NCI's experience initiating the ETCTN teaches several lessons.

First, it was important to select sites with significant drug development expertise and where many investigators had longstanding interactions, likely increasing their willingness to consider a team science approach and enroll patients in trials led by others. Second, the ETCTN required substantial investments in a centralized infrastructure to allow real-time data capture of critical measures such as patient accrual and adverse events and timely interventions to change trial design when needed. Assuring active participation among early career investigators and providing guidance for them through daunting, complex clinical trial development processes required additional resources. For example, the validation of predictive and prognostic biomarkers and their incorporation into early phase clinical trials across a multisite network is an enormously complex process requiring substantive education of PIs (even those with high levels of drug development expertise) and sufficient resources. Finally, it was critical to provide mechanisms to clearly communicate and maintain high awareness of the network's portfolio (active and pipeline) among PIs because they need early notice to balance NCI's trials within their organizations' portfolio.

During the 2020–2025 award period, the ETCTN will continue to leverage NCI resources to enhance early drug development productivity and will focus on three priorities. First, NCI actively aims to address the need to recruit rare or uncommon molecularly defined subsets of patients through new requirements, such as requiring each organization to have a minimum number of identified key investigators responsible for disease-specific accrual and providing partial salary to support additional team members. Second, NCI hopes to ensure the collection of high quality biopsy specimens, including providing partial salary support to include interventional radiologists and research pathologists on LAO teams. Finally, NCI will prioritize the use of biomarker assays to achieve precision medicine goals, with an increased use of NCI biomarker assay resources coordinated through the National Clinical Laboratory Network (NCLN) (see Table 1) while scaling back the UM1 biomarker assay development supplements and consolidating the ETCTN PK activities.

NCI's experience with the ETCTN shows that a national clinical trial network for early drug development is feasible, but required a substantial investment of resources and talent. As testing new anticancer agents increasingly depends on the identification of biomarkers and patients with specific molecular characteristics, research systems need to adopt efficient, cost-effective, and sustainable strategies. The ETCTN model capitalizes on NCI's long-term

support of a cancer center-based network of clinical researchers whose efforts can be marshalled, by providing centralized services, to efficiently and collaboratively design, implement, and complete early phase oncology clinical trials.

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TRANSLATIONAL RELEVANCE

NCI's experience with the ETCTN provides evidence that a national clinical trial network for early drug development is feasible, but has required a substantial investment of resources and talent. As testing of new anticancer agents becomes increasingly dependent on the identification of biomarkers and patients with specific molecular characteristics, research systems need to adopt strategies that are efficient, cost-effective, and sustainable. The ETCTN model capitalizes fully on NCI's long-term support of a cancer center-based network of clinical researchers whose efforts can be marshalled, through the provision of centralized services, to efficiently design, implement, and complete early clinical trials collaboratively.

Figure 1:

Patient accrual to ETCTN and legacy trials^a within the ETCTN, by Grant Year.

^aLegacy trials are those trials that had activated in NCI's previous early development program and transitioned into the ETCTN.

Figure 2:
 Network connectivity based on accrual to each other organizations' trials.
 Blue dots = LAOs; Red dots = Trials.
 Line thickness determined by the number of trials between two sites.

Table 1:
ETCTN Central Infrastructure & Biomarker Support

Service Name	Service Provided	Description of Service
Regulatory Support Services (RSS) ⁽¹⁾	Centralized repository of regulatory documents for ETCTN studies	Provides a streamlined and comprehensive approach to collecting and maintaining site registration, person, and institution documentation essential to the management of ETCTN studies.
CTEP Identity and Access Management (IAM) ⁽²⁾	Secure investigator and associate login to CTEP applications	Investigators and associates register with CTEP. IAM streamlines and provides access to CTSU applications utilizing unique usernames and passwords.
NCI Clinical Trials Support Unit (CTSUS) ⁽¹⁾	Centralized repository of all protocol-specific documents	Provides support to manage and conduct ETCTN trials, including roster data and a centralized repository for the regulatory documents.
NCI Central Institutional Review Board (CIRB) ⁽³⁾	Centralized IRB where NCI serves as IRB of record for all ETCTN studies	Provides human patient reviews for all ETCTN studies. Assures that the rights and welfare of humans who participate in ETCTN studies are protected.
Oncology Patient Enrollment Network (OPEN) ⁽⁴⁾	Web-based system for patient enrollment in real-time	Provides a web-based registration system for patient enrollment on a 24/7 basis to ETCTN trials
Protocol Authoring Contract	Protocol authoring service for ETCTN studies	NCI contracts science writers to work with the study team of an approved LOI to rapidly develop a high-quality protocol and reduce the number of revisions.
ETCTN Web Reporting (Medidata Rave) ⁽⁵⁾	Web-based system to report patient and safety information	Provides oversight of study safety and a secure audit trail of review history. Provides an interactive web-reporting tool that provides graphical and spreadsheet formats that capture all adverse event reporting from ETCTN trial case report forms in real-time.
CTEP Adverse Event Reporting System (CTEP-AERS) ⁽⁶⁾	Web-based system for CTEP monitoring and reporting of AEs	Provides an electronic platform that serves as the entry point for expedited adverse event reporting for all ETCTN trials.
Biomarker Support		
Biomarker Review Committee (BRC)	NCI committee to review and approve proposed biomarkers in trials	Reviews biomarker components of CTEP-funded clinical trials that are not reviewed by an NCI disease-specific steering committee
ETCTN Biorepository and Accessing Center	Storage and accessioning facility	Serves as a specimen storage facility and as an accessioning center to prepare clinical specimen for shipment
Cancer Immune Monitoring and Analysis Centers (CIMACS) Network ⁽⁷⁾	Network to facilitate correlative studies in clinical trials involving immunotherapy	Located at Dana-Farber Cancer Institute, Stanford University, MD Anderson, and Mount Sinai. Analyze tissue for genomic, phenotypic, and functional characterization of responses using analytically-validated and standardized platforms. Initiative of the NCI Cancer Moonshot.
PDXNet (Patient-Derived Xenografts Development and Trial Centers Research Network) ⁽⁸⁾	Network to coordinate large-scale development and pre-clinical testing of therapeutic agents in patient-derived models.	PDXNet is comprised of four PDC Development and Trial Centers (PDTs) and the PDX Data Commons and Coordinating Center (PDCCC).
Molecular Characterization (MoCha) lab	For genomic and transcription evaluation	Translates information using the characterization of molecular alterations in patients' tumors
Pharmacodynamic Assay Development and Implementation Section (PADIS) lab	For pharmacodynamic assays for evaluate mechanism of action and/or PD effects	A PD biomarker can be used to examine the link between drug regimen, target effect, and biological tumor response. Coupling new drug development with focused PD biomarker measurements provides critical data to make informed, early go/no-go decisions, to select rational combinations of targeted agents, and to optimize schedules of combination drug regimens.

Abbreviations: CTEP, Cancer Therapy Evaluation Program; NCI, National Cancer Institute, ETCTN, Experimental Therapeutics Clinical Trials Network

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Table 2:

ETCTN Clinical Trial Performance over first grant funding cycle grant years (GY)

LETTER OF INTENT (LOI)	GY1-GY5 Total	GY1	GY2	GY3	GY4	GY5
# LOIs submitted to ETCTN	334	64	49	72	69	80/60 ^a
# Approved LOIs	132	13	23	29	33	34
Project Team LOIs	63	1	13	17	14	18
Unsolicited LOIs	69	12	10	12	19	16
LOI Approval Rate	42%	20%	47%	40%	48%	57%
# (%) LOIs led by early career PIs	141 (42%)	25 (39%)	20 (41%)	33 (46%)	28 (42%)	35 (44%)
TRIAL ACTIVATION	GY1-GY5 Total	GY1	GY2	GY3	GY4	GY5
# trials activated within ETCTN	102	6	16	26	29	25
Avg # trials activated at LAO/AO	4.4	<1	2	3	6	10
PROJECT TEAMS	GY1-GY5 Total	GY1	GY2	GY3	GY4	GY5
# Project Teams started	19	4	3	2	5	5
Average # Months between approval for Project Team and first LOI submitted	7.8	7.5	9.6	8.5	7.6	6.5
Targets		HSP90; EGFR; ATR; EGFR	PD-L1; PD-L1; MDM2	Oncolytic Virus; anti- mesothelin ADC	glutaminase; PI3K; proteasome; NAE; DNA-PK	radio-pharmaceutical; FGFR; FGFR; anti- HER2 ADC; E- selectin

^a At the time of reporting, GY5 had 34 approved LOIs, 26 disapproved LOIs, and 20 in review; the denominator to calculate the approval rate was 60 LOIs with a known status.

^b Legacy trials are those trials that had activated in NCI's previous early development program and transitioned into the ETCTN.