Check for updates

editorials

The National Clinical Trials Network: A Valuable and Undervalued Resource

Howard A. Burris III, MD[1]

In the 50 years since the signing of the National Cancer Act in 1971, the National Cancer Institute's (NCI) National Clinical Trials Network (NCTN) has been conducting studies resulting in important discoveries for improving the care of patients with cancer. The current four cooperative groups (Alliance; Eastern Cooperative Oncology Group-American College of Radiology Imaging Network [ECOG-ACRIN]; National Surgical Adjuvant Breast and Bowel Project, Radiation Therapy Oncology Group, and Gynecologic Oncology Group [NRG]; and SWOG) plus one pediatric group (Children's Oncology Group [COG]) that make up the structure of the NCTN (see Fig 1) are the result of a reorganization orchestrated by the NCI in 2010. The American College of Surgeons Clinical Oncology Group, the Cancer and Leukemia Group B (CALGB), and the North Central Cancer Treatment Group merged into a single entity, the Alliance for Clinical Trials in Oncology. The ECOG merged with the ACRIN and became the ECOG-ACRIN Cancer Research Group. The National Surgical Adjuvant Breast and Bowel Project, the Radiation Therapy Oncology Group, and the Gynecologic Oncology Group formed the NRG Oncology Group. The Southwest Oncology Group was renamed the SWOG Cancer Research Network and the Children's Oncology Group continued, previously having merged four pediatric groups in 2000 (Fig 1). With more than 2,000 sites across the country, the network provides an inherent and remarkable diversity among our physicians and patients. Funded by the federal government, the NCTN offers a system to explore and assess many clinical cancer care questions that may have a substantial impact on the lives of patients but unlikely to derive commercial benefit to any one company.

In the article that accompanies this editorial, Unger et al[1] described the impact of positive clinical trials conducted by the NCTN. The conclusions are drawn from the survival impact documented across a variety of malignancies by the various cooperative groups. In addition, the cost benefit analyses emphasize both the value of the NCTN as well as highlighting the potential advantages for greater investment.

The advent of easily accessible next-generation sequencing, the discovery of actionable mutations (still often uncommon), and the rapid development of novel molecular entities has changed the paradigm of drug development. The pursuit of single-arm trials sponsored by pharmaceutical and biotech companies leading to rapid regulatory approvals is the new standard and expectation for new agents in many cancer subtypes. Efficient and effective drug development is an appropriate and valuable approach in these settings where a targeted therapy is being assessed.[2] More than 60 regulatory approvals have resulted from this process over the past 10 years but frequently with accelerated status on the basis of objective response rates versus an overall survival, or even progression-free survival, end point. It is thus not surprising to see the number of positive trials included in the analysis by Unger et al[1] to be diminished during the past decade.

The high risk and high reward space of early drug development is best served by the capital markets to sort out the winners and losers as quickly as possible. The past few years have seen more than 500 Investigational New Drug applications filed annually with the Food and Drug Administration to initiate trials with an experimental agent, with most progressing to phase I trials. This progression results in substantial competition in the United States and globally for sites and access to patients. For those fortuitous agents that eventually receive regulatory approval and commercial success, decisions must then be made regarding investments into clinical trials exploring additional tumor types, combination regimens, and other areas such as pediatric tumors or rare cancers. The length of the patent life is often a crucial factor in making substantial investment decisions.

Randomized phase III studies are the standard on which to establish a survival benefit, and an improvement in overall survival is the goal of both cancer researchers and pharmaceutical companies in developing a new agent. Although an initial phase III study is often company sponsored, numerous factors comprise the decision to conduct additional lengthy and expensive trials in other disease settings or tumor types including patent life, return on investment, and opportunity cost. The role of the NCTN is vital to exploring these therapies fully and to study factors ranging from the comparison of similar agents to de-escalation of therapy to neoadjuvant and adjuvant settings.

In a retrospective cohort study evaluating phase III SWOG Cancer Research Network Trials between 1980 and 2017, the positive (and negative) results of nearly

ASSOCIATED CONTENT

See accompanying article on page 2020

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on January 4, 2023 and published at ascopubs.org/journal/jco on February 27, 2023: DOI https://doi.org/10.1200/JCO.22.02628

© 2023 by American Society of Clinical Oncology

Downloaded from ascopubs.org by Johns Hopkins University School of Medicine on April 14, 2023 from 162.129.250.058
Copyright © 2023 American Society of Clinical Oncology. All rights reserved.

THE TAKEAWAY

In the article that accompanies this editorial, Unger et al[1] describe the impact of the National Clinical Trials Network in terms of the positive phase III trials conducted. The clinical and scientific results are measured in terms of additional life-years to patients with cancer at a remarkably low cost.

half of all phase III trials were practice influential, meaning they were associated with changes in National Comprehensive Cancer Network clinical guidelines or new drug indications approved by the US Food and Drug Administration.[3] An example of a recent practice influential trial is the E3805 CHAARTED trial, which confirmed the benefit of docetaxel in combination with androgen-deprivation therapy for high-volume disease subgroup of patients with metastatic hormone-sensitive prostate cancer.[4] Most recently, results from the randomized phase II SWOG S1801 study presented at the 2022 European Society of Medical Oncology Meeting suggest that neoadjuvant pembrolizumab followed by adjuvant pembrolizumab improves event-free survival in resectable melanoma as compared with the same treatment given entirely in the adjuvant setting.[5] Finally, and equally important, CALGB/SWOG 80405 (Alliance) established the significance of sidedness as an independent prognostic factor in patients with metastatic colorectal cancer.[6]

The US health care system often leads the way for the development and approval of new agents. In addition, utilization of these therapies in the United States establishes new standards and guidelines for patients with cancer in other countries. Much learning is derived from randomized trials after drugs are initially approved, including negative studies that are often not as newsworthy. Comparisons among classes of drugs such as the checkpoint inhibitors, the CDK 4/6 inhibitors, the PARP inhibitors, among others will generally need to be studied by nonpartisan groups such as the NCTN. Noninferiority designs might be appropriate for some of these clinical questions but often require larger numbers of participants and longer follow-up for statistically valid results.

It is a simple fact that commercial entities are not incentivized to give less of a therapy or regimen, whether that is prescribing 3 or 6 months of an adjuvant treatment or

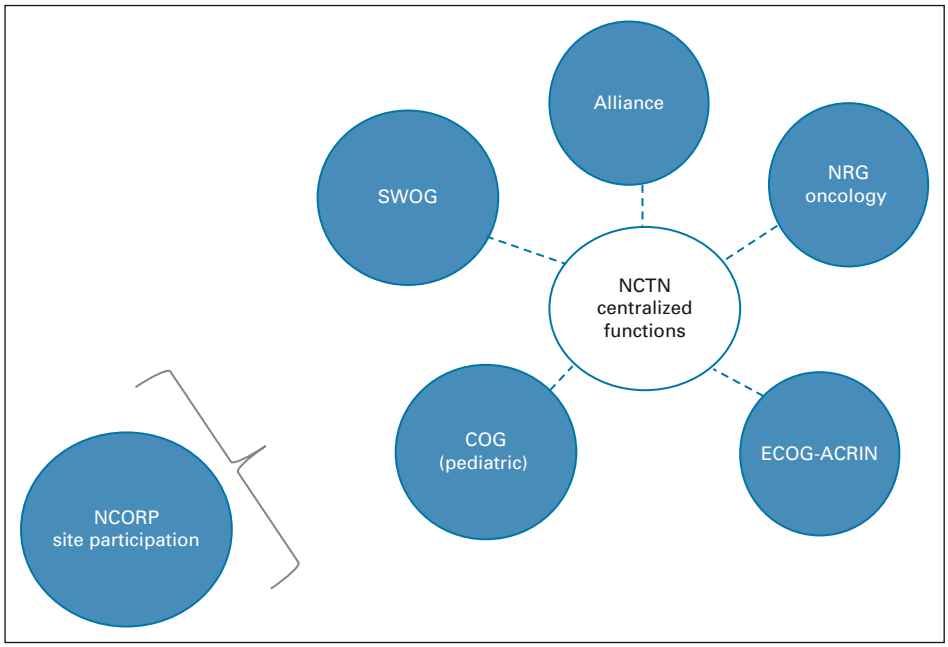

FIG 1. NCI's NCTN is a group of sites and physicians that conduct cancer clinical trials at more than 2,200 sites across the United States, Canada, and internationally. NCTN provides the infrastructure for NCI-funded treatment studies designed to improve the lives of people with cancer. ACRIN, American College of Radiology Imaging Network; COG, Children's Oncology Group; ECOG, Eastern Cooperative Oncology Group; NCI, National Cancer Institute; NCORP, NCI Community Oncology Research Program; NCTN, National Clinical Trials Network; NRG, National Surgical Adjuvant Breast and Bowel Project, Radiation Therapy Oncology Group, and Gynecologic Oncology Group.

Downloaded from ascopubs.org by Johns Hopkins University School of Medicine on April 14, 2023 from 162.129.250.058
Copyright © 2023 American Society of Clinical Oncology. All rights reserved.

limiting the duration of a maintenance therapy or even discontinuing agents in the setting of a complete remission.

Unger et al[1] have taken on an ambitious question in attempting to describe the impact of the NCTN. Using only positive studies of experimental therapies to assess prolonged life for cancer patients might seem unorthodox at first glance. Negative trials will also have an impact and dissuade the use of new agents inappropriately. To measure the inclusion of results in package inserts or guidelines requires a positive result. Similarly, to measure the increase in life-years for patients benefiting from the NCTN studies also necessitates a positive end point, with the remarkable assessment that federal investment costs were $326 in US dollars per life-year gained. Financial conclusions are difficult to reach as so many factors go into the true cost of any work performed, but regardless, even if the results are off by a factor of 10 or more, the investment pales in comparison with the impact.

Not to be forgotten in the discussion over the value of the NCI-funded NCTN are the numerous surgical, radiation, and cancer control and prevention studies that would struggle to be performed through any other mechanism. These studies are now funded by the NCI Community Oncology Research Program, a network bringing cancer care delivery and clinical trial studies to people in their communities. The impact of minimizing surgical approaches (lumpectomy, sentinel node mapping, sphincter sparing, etc) on quality of life and comorbidities is profound, as are the benefits of combined modality therapy in many cancer settings (head and neck, lung, rectal, anal, etc).

The continuation and acceleration of funding for the NCTN to conduct a robust menu of clinical trials in a variety of cancer and disease settings will be critical for improving the care of and outcomes for patients with cancer. On October 16, 2022, Monica Bertagnolli, MD, oncology surgeon, became the 16th director of the NCI. In addition to her outstanding career at Harvard and Brigham and Women's Hospital in Boston, Dr Bertagnolli brings a long history with the cooperative groups, including a 10-year term as chairperson for Alliance (CALGB). Her unique understanding of the importance of these contributions will hopefully lead to greater investment. Ongoing and future directions such as the diversity, equity, and inclusion initiatives, central institutional review board, broadening eligibility criteria, and streamlining enrollment will certainly be emphasized under her leadership. This network will also be a source of success to increase diversity and include rural, minority, and other underserved populations in potentially practice-changing studies. The dollars spent versus the impact delivered is remarkably disproportionate. In addition, well-designed studies from the NCTN will provide benefits in delivering cost-effective care while maximizing the continued improvements in cancer outcomes. The network is clearly valuable in innumerable ways, and we must not undervalue it through insufficient funding to conduct this important work.

AFFILIATION

[1]Sarah Cannon Research Institute, Nashville, TN

CORRESPONDING AUTHOR

Howard A. Burris III, MD, Sarah Cannon Research Institute, 1100 Dr Martin Luther King, Jr. Boulevard Ste 800, Nashville, TN 37203; e-mail: Howard.burris@sarahcannon.com.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the author are available with this article at DOI https://doi.org/10.1200/JCO.22.02628.

REFERENCES

1. Unger JM, LeBlanc M, George S, et al: Population, clinical, and scientific impact of National Cancer Institute's National Clinical Trials Network treatment studies. J Clin Oncol 41:2020-2028, 2023
2. Prowell TM, Theoret MR, Pazdur R: Seamless oncology-drug development. N Engl J Med 374:2001-2003, 2016
3. Unger JM, Nghiem VT, Hershman DL, et al: Association of National-Cancer Institute-Sponsored Clinical Trial Network Group studies with guideline care and new drug indications. JAMA Netw Open 2:e1910593, 2019
4. Kyriakopoulos CE, Chen YH, Carducci MA, et al: Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: Long-term survival analysis of the randomized phase III E3805 CHAARTED trial. J Clin Oncol 36:1080-1087, 2018
5. Patel S, Othus M, Prieto V, et al: LBA6: Neoadjuvant versus adjuvant pembrolizumab for resected stage III-IV melanoma (SWOG S1801). Ann Oncol 33: S808-S869, 2022 (suppl 7)
6. Venook AP, Ou FS, Lenz HJ, et al: Primary tumor location as an independent prognostic marker from molecular features for overall survival in patients with metastatic colorectal cancer: Analysis if CALGB/SWOG 80405 (Alliance). J Clin Oncol 35:3503, 2017 (suppl 15)

Downloaded from ascopubs.org by Johns Hopkins University School of Medicine on April 14, 2023 from 162.129.250.058
Copyright © 2023 American Society of Clinical Oncology. All rights reserved.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The National Clinical Trials Network: A Valuable and Undervalued Resource

The following represents disclosure information provided by the author of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Howard A. Burris III
Employment: HCA Healthcare
Leadership: HCA Healthcare
Stock and Other Ownership Interests: HCA Healthcare
Research Funding: Roche/Genentech (Inst), Bristol Myers Squibb (Inst), Incyte (Inst), AstraZeneca (Inst), MedImmune (Inst), Macrogenics (Inst), Novartis (Inst), Boehringer Ingelheim (Inst), Lilly (Inst), Seattle Genetics (Inst), Merck (Inst), Agios (Inst), Jounce Therapeutics (Inst), Moderna Therapeutics (Inst), CytomX Therapeutics (Inst), GlaxoSmithKline (Inst), Verastem (Inst), Tesaro (Inst), BioMed Valley Discoveries (Inst), TG Therapeutics (Inst), Vertex (Inst), eFFECTOR Therapeutics (Inst), Janssen (Inst), Gilead Sciences (Inst), BioAtla (Inst), CicloMed (Inst), Harpoon therapeutics (Inst), Archer (Inst), Arvinas (Inst), Revolution Medicines (Inst), Array BioPharma (Inst), Bayer (Inst), Kymab (Inst), Pfizer (Inst), Takeda/Millennium (Inst), Foundation Medicine (Inst), EMD Serono (Inst), ARMO BioSciences (Inst), CALGB (Inst), Hengrui Therapeutics (Inst), XBiotech (Inst), Zymeworks (Inst), Coordination Pharmaceuticals (Inst), NGM Biopharmaceuticals (Inst), Gossamer Bio (Inst), Ryvu Therapeutics (Inst), BioTheryX (Inst), AbbVie (Inst), BeiGene (Inst)
Uncompensated Relationships: Bayer (Inst), GRAIL (Inst), Novartis (Inst), Vincerx Pharma (Inst), AstraZeneca (Inst), Incyte (Inst), Bristol Myers Squibb (Inst), Boehringer Ingelheim (Inst), TG Therapeutics (Inst)
Open Payments Link: https://openpaymentsdata.cms.gov/physician/201030

No other potential conflicts of interest were reported.

Downloaded from ascopubs.org by Johns Hopkins University School of Medicine on April 14, 2023 from 162.129.250.058
Copyright © 2023 American Society of Clinical Oncology. All rights reserved.