NCI National Clinical Trials Network (NCTN) Concept for RFA Reissuance

15th Joint Meeting of NCI BSA/NCAB
Meg Mooney, MD
June 15, 2023

Cancer Therapy Evaluation Program
Division of Cancer Treatment & Diagnosis
National Cancer Institute

NIH NATIONAL CANCER INSTITUTE

Transformation of former Cooperative Group program to NCI National Clinical Trials Network (NCTN) 2014

Establish/Support programmatic infrastructure to:

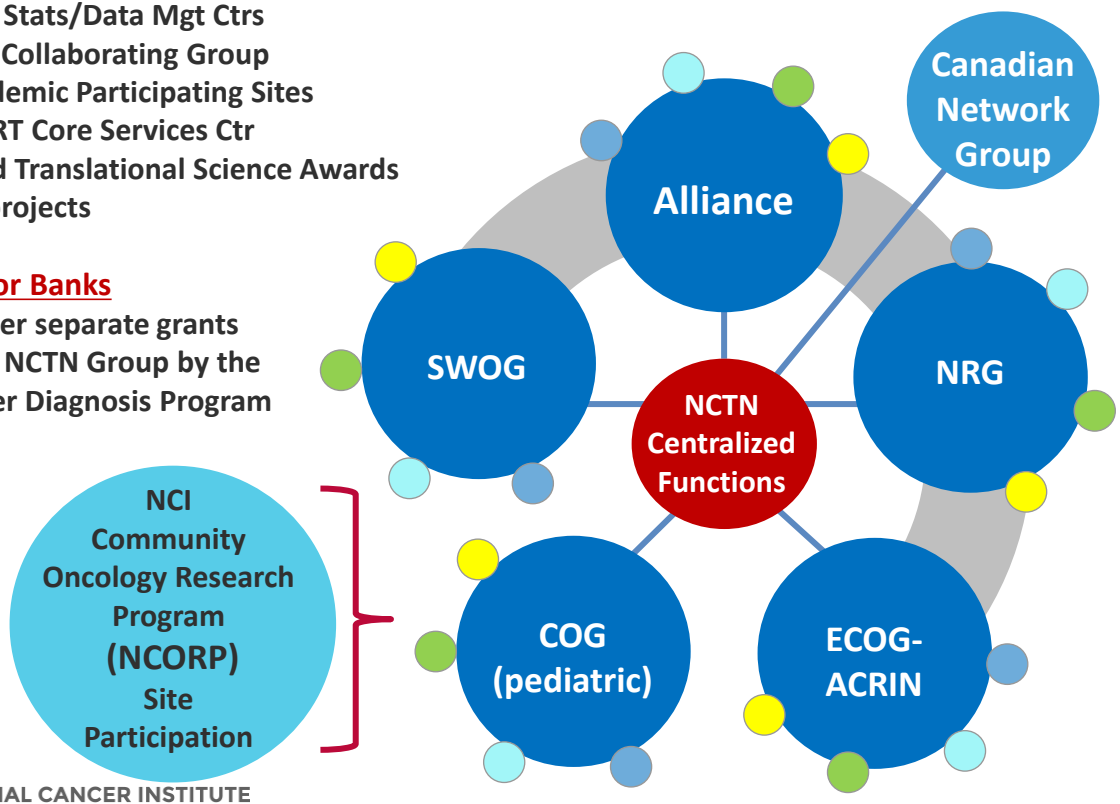
- Harmonize processes & promote collaborations
- Focus on questions not well supported in commercial environment
- Prioritize trials & incorporate innovative science and design
- Provide large-scale testing of molecularly-defined cancers & incorporate "*precision medicine"* into portfolio, along with rare tumor trials
- Maintain commitment to conduct trials in diverse & special populations

NCTN Program Organizational Structure

6 RFAs:

- US Group Operation Ctrs
- US Group Stats/Data Mgt Ctrs
- Canadian Collaborating Group
- Lead Academic Participating Sites
- Imaging/RT Core Services Ctr
- Integrated Translational Science Awards for pilot projects

NCTN Tumor Banks
funded under separate grants for each US NCTN Group by the DCTD Cancer Diagnosis Program



LEGEND:

Centralized Functions:
- NCI CIRB with 4 Boards
- Cancer Trials Support Unit
- RT/Image Core Ctr (IROC)
- NCI Disease Committees
- Common Data Mgt System w/ Central Hosting (RAVE)

Lead Academic Participating Sites (LAPS)

Operations Centers

Statistics & Data Mgt

Tumor Banks

CTEP CORE for Clinical Trials Helps Support NCTN
& Other NCI-funded clinical trials networks

Contracted support in following domains:

- **Information Security**
- **Study Administration & Logistics**
- **Clinical Data Capture & Reporting**

  Enrollment, Medidata Mgt System

- **Regulatory Monitoring & Reporting**

  Investigator Credentialing
  NCI CIRB & Regulatory Support
  IND Sponsor Activities for Selected NCTN Trials

- **Data Quality & Control**
- **Correlative Study Data**

NCTN Program Organizational Structure

Large Umbrella/Basket Trials Requiring National Catchment Area

ADULT & PEDIATRIC MATCH (Target Therapies Across Histologies)

LUNG MAP, ALCHEMIST (Target Therapies in Adv & Early Lung Cancer

NEW Precision Medicine Trials: ComboMATCH, myeloMATCH, iMATCH

Multimodality & Non-Drug Trials

Role of Weight Loss in Treatment of Early Breast Ca

Dose-Escalated RT +/- ADT in Intermediate Prostate Ca

Combination Therapy Trials

Chemo + Immunotx in Resected Stage III Colon Ca dMMR

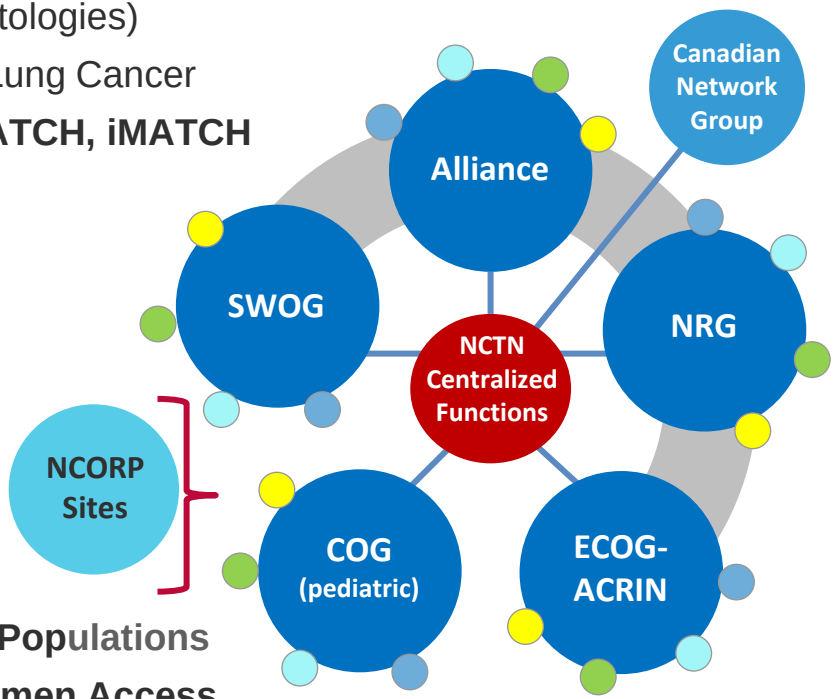
Special Populations & Initiatives

AYA Trials, Broadening Eligibility & Outreach to Diverse Populations

NCTN/NCORP Data Archives & NCTN Navigator Biospecimen Access

Longitudinal Natural Hx Study of COVID-19 in Cancer Patients (NCCAPS)

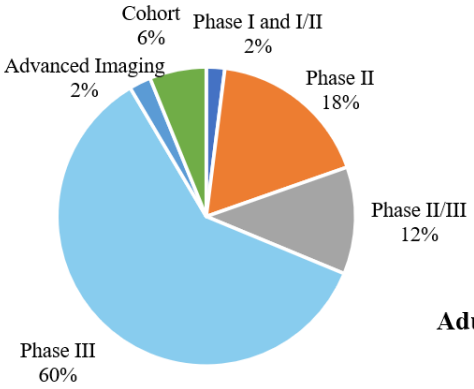
Real World Trials: Launch of Pragmatica-Lung



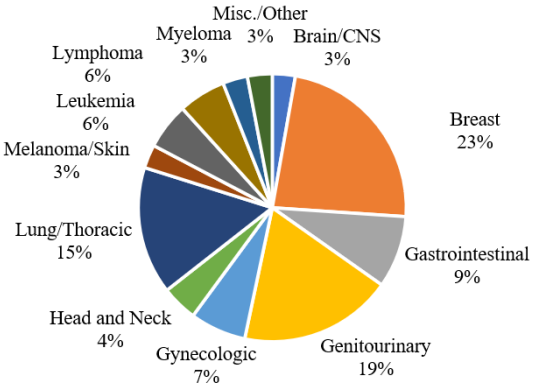
Adult/Pediatric Intervention Accruals: Trial Phase & Cancer Type
(3/1/2019 to 10/31/2022)

All Trials
IND: 65%
Non-IND: 35%

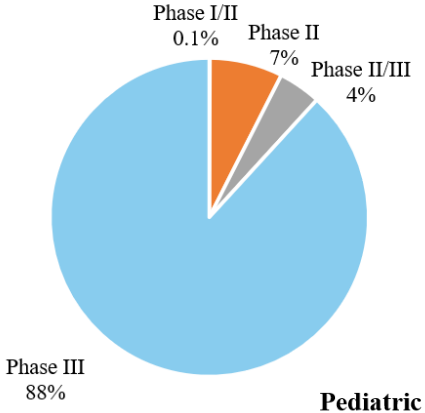
Adult Intervention/Cohort Accrual



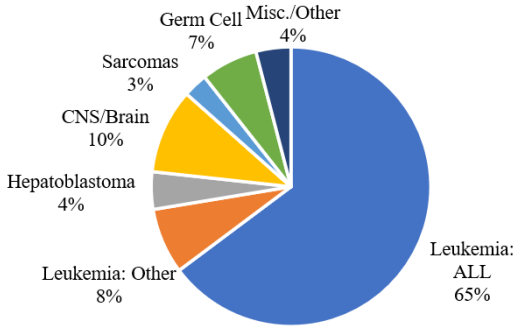
Adult Intervention/Cohort Accrual



Pediatric Intervention/Cohort Accrual

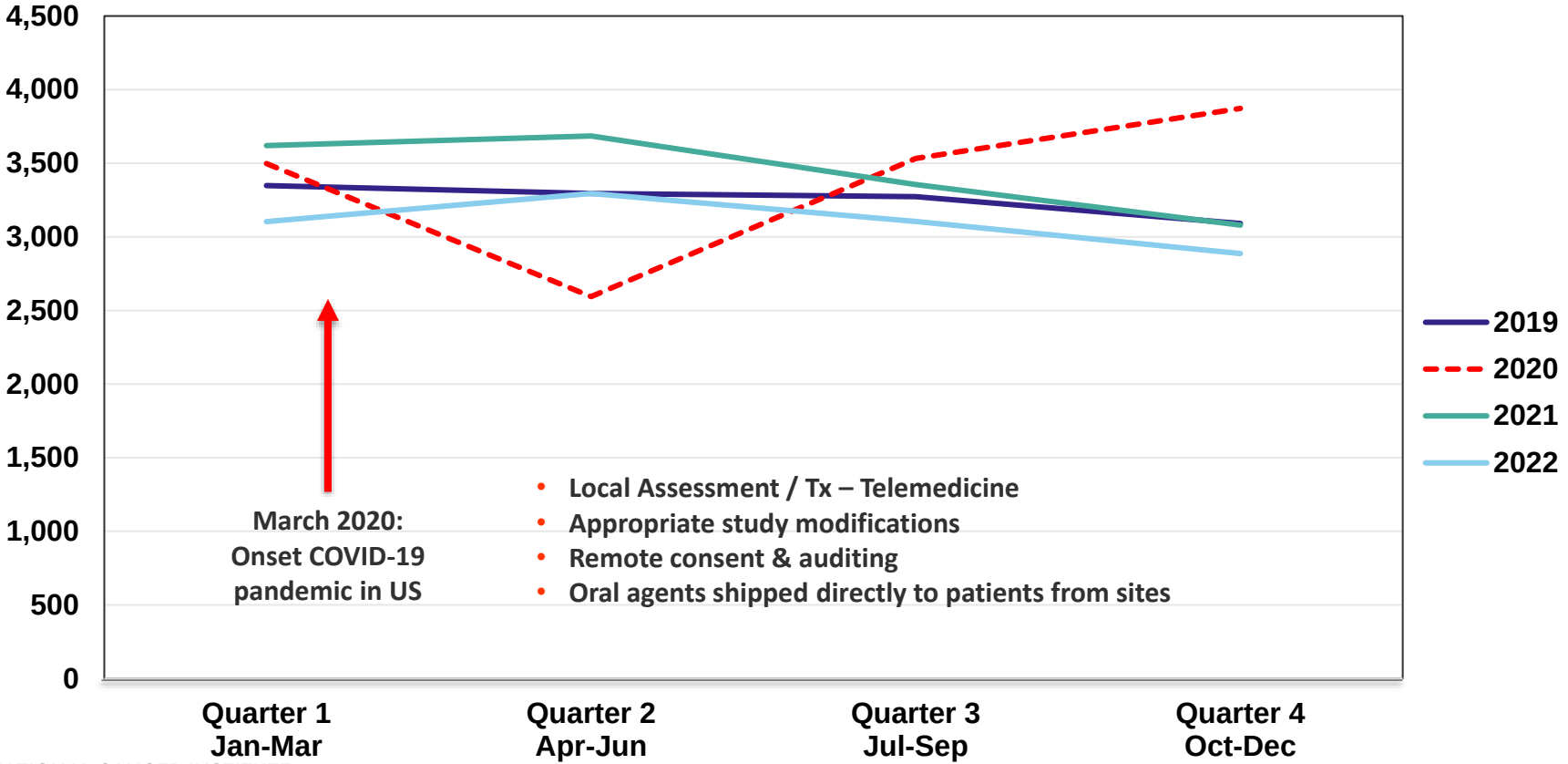


Pediatric Intervention/Cohort Accrual

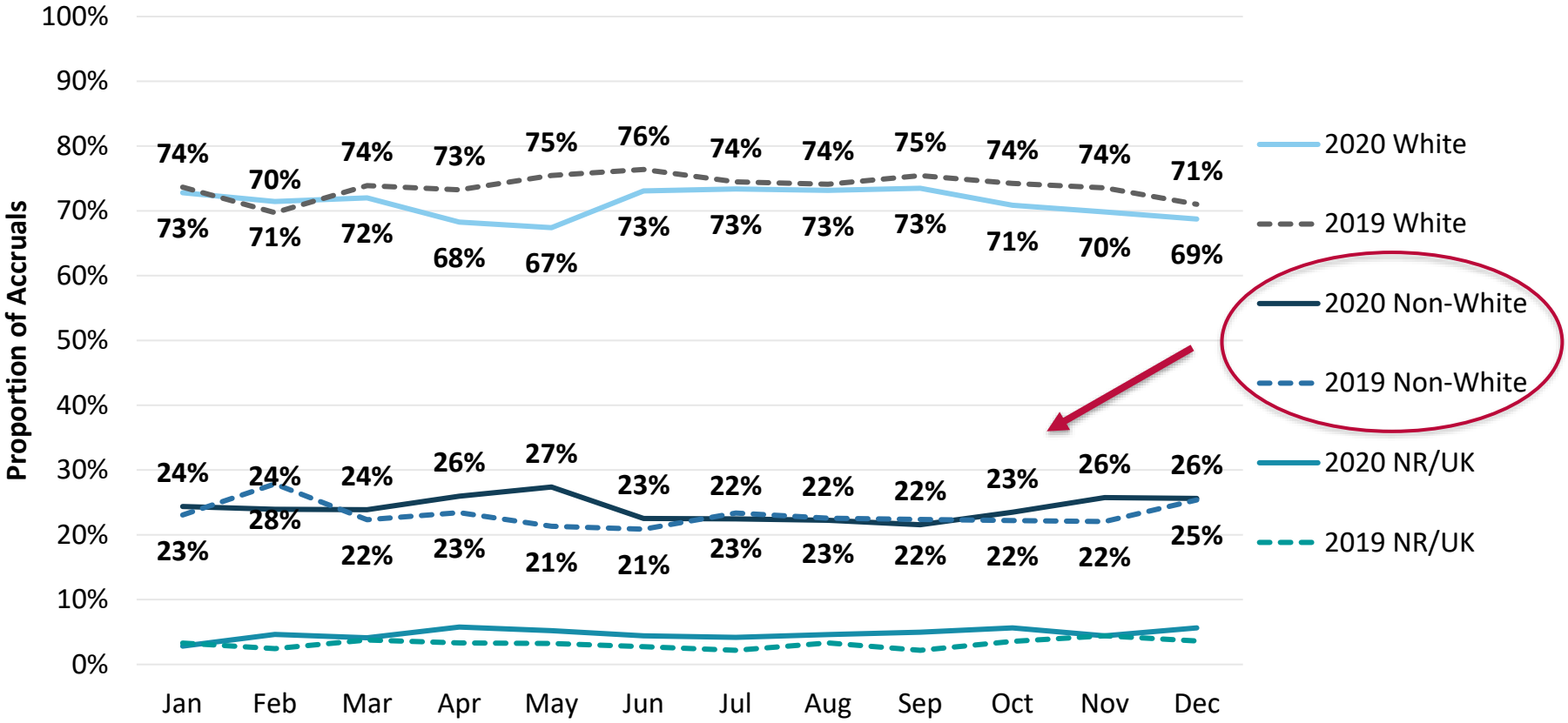


Special Consideration for Project Period: COVID-19 Pandemic

NCTN Quarterly Intervention Accrual to Treatment Trials 2019-2022



NCTN 2019 and 2020 Accrual by Month
Proportion of Participants who were White or Non-White



NCTN Study Components & Accrual

	Study Component & Accrual by Project Period	
NCTN Study Component	**Project Period 1 (60 Months) "Annual Avg"**	**Project Period 2 (44 Months) "Annual Avg"**
# LOI & Concept Approval	51	51
# Trial Activations	46	43
NCTN Accrual Component	**Project Period 1 "Annual Avg"**	**Project Period 2 "Annual Avg"**
# Accruals: Screen on Study	5,494	4,004
# Accruals: Intervention/Cohort	15,180	13,533
# Accruals – Total Accrual	20,674	17,537

Period 1 "screening on study" accruals include Adult & Pediatric MATCH.
Period 2 accrual includes COVID-19 NCCAPS study. Period 2 decreased by ≈10.8% due to pandemic.

NCTN Accrual by Enrolling Site Types

	2nd Project Period Intervention Accruals by Full Member Site Type (3/1/2019-10/31/2022)		
Site Type (with integral subsites)	# Sites	% All Accruing Sites	% All Accruals
LAPS	198	12.9%	28.3%
NCORP	623	40.6%	27.7%
Rostered	713	46.5%	44.0%

1,600 sites had accruals registered to NCTN in 2nd project period to 287 Trials
Composed of 1,439 US sites & 161 international sites (including non-member collaborators)

Key Accomplishment:
Conduct of Collaborative Trials in Special Populations - AYA

S1826: Phase 3 Randomized Study of Nivolumab + AVD or Brentuximab Vedotin + AVD in Patients (Age >/= 12 Years) with Newly Diagnosed Advanced Stage Classical Hodgkin Lymphoma

Study Opened: July 2019
Study Closed: Dec 2022
994 Patients Enrolled (M/F: 45% vs 55%)

- **12 – 17 yrs: 24%**
- **18 – 60 yrs: 66%**
- **Over 60 yrs: 10%**

White 76%, Black, 12%, Asian 3%; Hispanic 13%

Results Presented 2023 ASCO Plenary Session

J Clin Oncol 41, 2023 (suppl 17; abstr LBA4)

- N-AVD improved progression-free survival (PFS) compared to Bv-AVD as initial treatment of advanced stage cHL
- N-AVD was well-tolerated
  - Few immune-related adverse events
  - < 1% of patients received radiation therapy (RT)
- Key step towards harmonizing pediatric and adult therapy of cHL
- **N-AVD is poised to be a new standard for treatment of advanced stage cHL**

Key Accomplishment:
Question Not Well-supported in a Commercial Environment

PROSPECT: Alliance N1048

PreOp Chemotx w/ Selective ChemoRT *versus* ChemoRT for Patients with Locally Adv Rectal Cancer

Study Activation: Jan 2012
Closed Accrual/Tx: Nov 2019
Total Enrollment: 1,194 patients

Non-inferiority Trial

Compare standard 5FUCMT to neoadjuvant FOLFOX followed by selective use of 5FUCMT with respect to the co-primary endpoints of Time to Local Recurrent & Disease-free Survival

Most Intermediate rectal cancer patients can receive curative-intent treatment without pelvic chemoradiation

- **Clinical Correlatives:** Quality of Life (QOL) & Patient Report Outcomes (PROs)
- **Immunologic Studies:** Indicators of Immunologic Activation
- **Pharmacogenomics:** Germline Variation as a Predictor of Response & Toxicity to Platinum-based Chemotx & RT

Results Presented 2023 ASCO Plenary Session & Simultaneous NEJM Publication

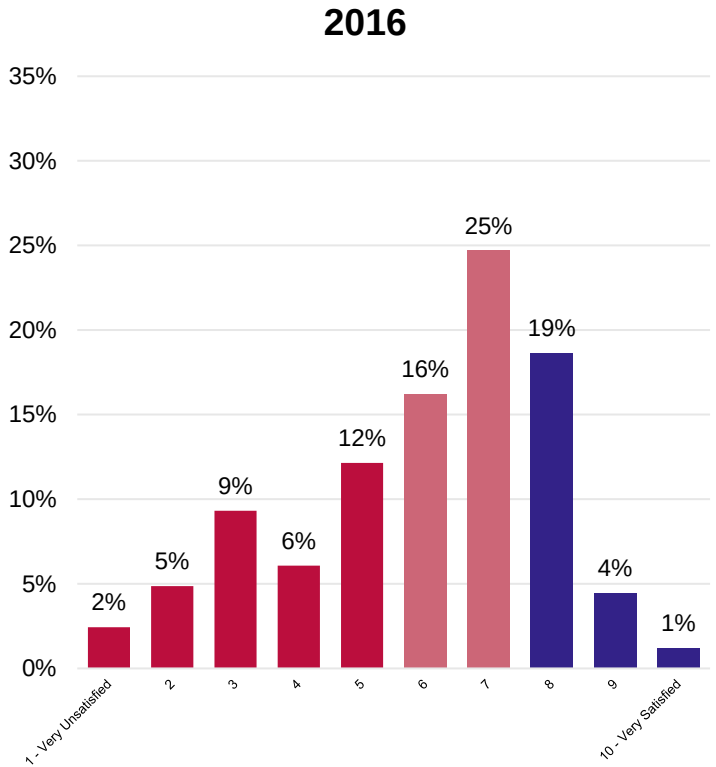
J Clin Oncol 41, 2023 (suppl 17; abstr LBA2)

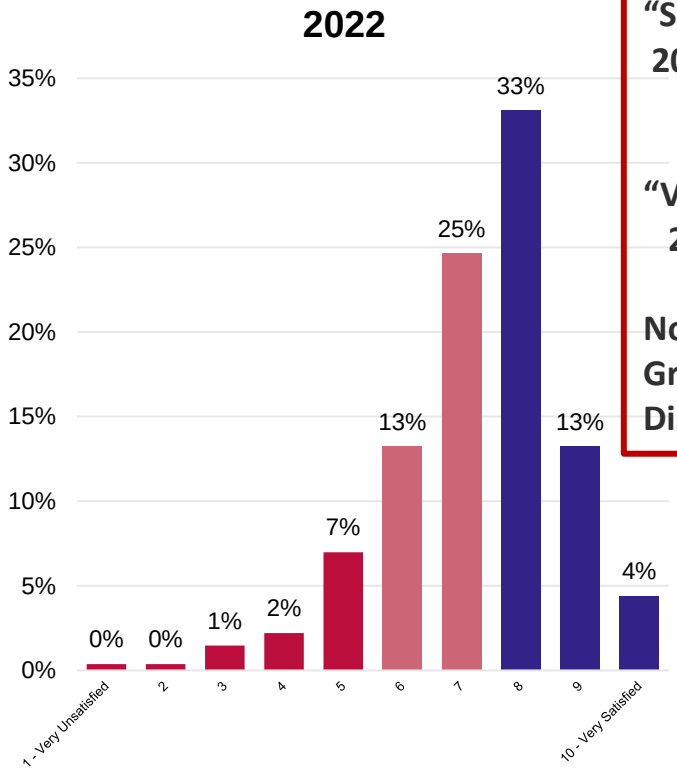
Other Selected Recent Key Accomplishments - Results

Trial	Impact / Accomplishment
AHOD1331: Randomized Phase 3 Study of Brentuximab Vedotin for Newly Dx'ed **High-Risk Classical Hodgkin Lymphoma in Children & Young Adults**	Patients receiving brentuximab vedotin with chemotherapy had a **Superior 3-year Event-Free Survival** (92.1%) compared to those who did not receive the agent (82.5%) with no increase in toxicity. **NEJM Publication & FDA Approval of Indication Nov 3, 2022.**
E1910: Phase 3 Randomized Trial of Blinatumomab for Newly Diagnosed BCR-ABL-Negative B Lineage **Acute Lymphoblastic Leukemia in Adults**	Blinatumomab added to consolidation chemotherapy led to significantly **Better Overall Survival** in pts with newly dx'ed B-cell ALL who were MRD negative after intensification chemotx (median OS: not reached vs 71.4 months, HR 0.42, 95% CI: 0.24 - 0.75; two-sided p=0.003). Median F/U of 43 months. Represents new standard for BCR::ABL1 negative ALL adult patients 30-70 yrs. **Late Breaking Abstract Session ASH Annual Mtg Dec 6, 2022. Designed as a Registration Intent Study for FDA Approval in Indication.**
NRG-GY018: Randomized, Placebo-Controlled Study of Pembrolizumab in Addition to Paclitaxel & Carboplatin for Measurable Stage III or IVA, Stage IVB or **Recurrent Endometrial Cancer**	Pembrolizumab in combination with chemotherapy resulted in a significantly **improved Progression-free Survival (PFS)** in dMMR cohort of 74% compared to 38% in placebo group (HR, 0.30; 95% CI 0.19 to 0.48; P<0.001). In pMMR cohort, median PFS was 13.1 months *vs* 8.7 months (HR, 0.54; 95% CI, 0.41 to 0.71; P<0.001). **Presented Annual SGO Mtg with NEJM publication on Mar 27, 2023. Designed as Registration Intent Study for FDA Approval in Indication.**

Survey of Key NCTN Participants: Satisfaction Has Improved

Overall Satisfaction with the NCTN: December 2016 vs. August 2022





"Satisfied" range (6-10)
2016: 65% → 2022: 89%

"Very satisfied" range (8-10)
2016: 24% → 2022: 51%

No differences based on Group Affiliation, Role, or Disease Area for 2022

External Evaluation Panel: NCTN Assessment

Many highly significant, practice-changing trials in various cancers conducted, which they considered best marker of NCTN success & many would not have been performed by industry or without public funding:

- evaluation of agents from different companies
- difficult randomized comparisons of surgery, RT, and/or drug tx *vs* no tx or modified tx
- studies in rare tumors & common cancer rare subsets & de-escalation strategy trials

Panel highly supportive of other NCTN components, including LAPs, IROC, ITSAs

In concluding remarks, 1 panel member stated following that was echoed by others:

"This is an unbelievable program. There is no question, one of the best in the world. There is no comparison with anything else in terms of [its] enormous size, extent, and depth. All our colleagues who helped create and manage this program absolutely deserve congratulations."

External Panel's Key Concerns/Recommendations

- Increases in funding are **critical** to continued high-level performance
- Trials should be designed with challenges for accrual burden on sites in mind & flexibilities implemented during COVID-19 should continue
- Enrollment of diverse populations needs improvement & prioritization
- NCTN Groups & NCI should continue to accelerate trial development
- Enhance collaboration so Network can engage in successful initiatives together (outreach to diverse patients, EMR pilots, workforce diversity).

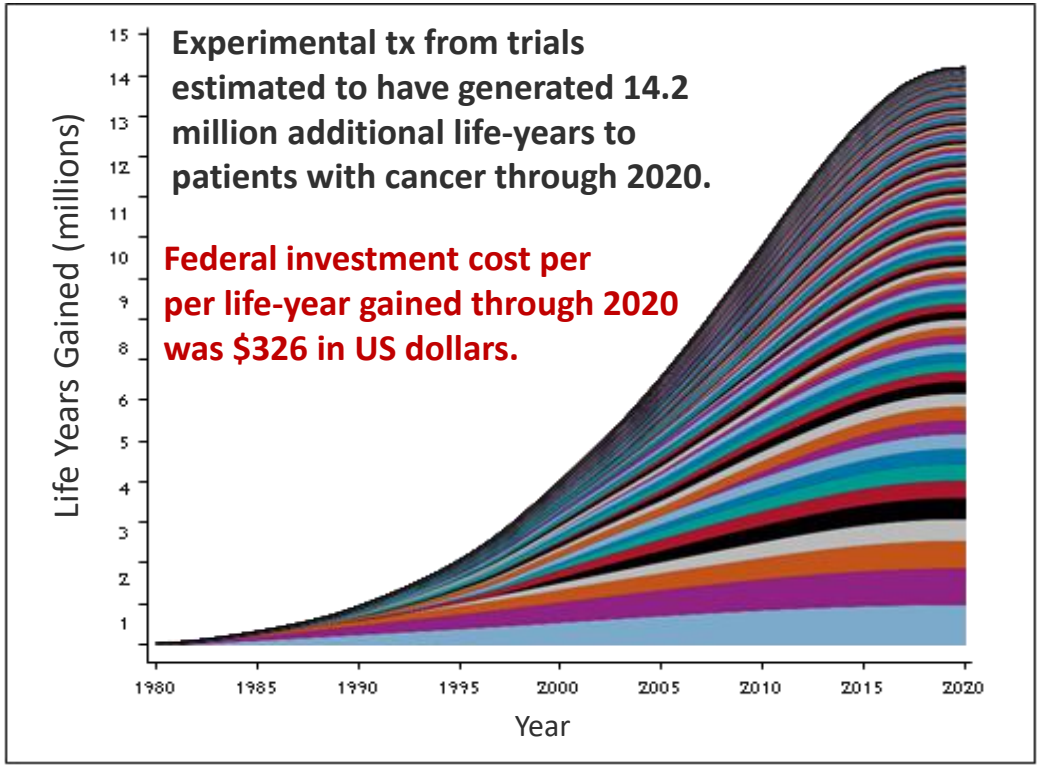
Population, Clinical, and Scientific Impact of National Cancer Institute's National Clinical Trials Network Treatment Studies

Unger JM et al, JCO, 2023 Apr 10;41(11):2020-2028. doi: 10.1200/JCO.22.01826. Epub 2022 Dec 8.

162 Adult NCTN positive, randomized trials since 1980 analyzed comprising 108,334 patients. Trials cited 165,336 times thru 2020, with 87.7% cited in cancer care guidelines favoring recommended tx.

Relevance: Impact of US NCTN trials on adult cancer outcomes cannot be overstated; this evidence should compel sustained financial investment and continued academic contributions to this valuable resource.*

*Relevance section written by *JCO* Editor-in-Chief Jonathan W. Friedberg, MD.



Cumulative life-years gained through 2020 by Study

Budget Considerations

- Funding cited by Extramural Community & External Review Panel as most critical need.
- Accrual already reduced from a decade ago (pre-NCTN) by ≈ 20% & services centralized. Even with more centralization & streamlining of trials, significant resources are needed to preserve the program, especially w/ rising costs & loss of health care and research staff.
- Rough comparisons of "per patient accrual" cost for NCTN *vs* industry trials are below.

AACI Survey of Academic Cancer Centers Support for Trial Offices (CTOs) *

Sponsor Type	Median % Trials	Median % Accrual	Median % Budget
Industry	43%	39%	45%
National Coop Grp	33%	19%	4%
Institutional	15%	33%	0%
External	4%	5%	3%

***Lee C, et al. Oncology Practice 2021 17:1, e77-e93**

Comparison to Industry CRO estimated Per Patient "Pivotal Trial" Cost in Oncology *

CRO Median US $100,242 ($80,800 to $155,414)

Comparable estimate for NCTN's estimated "Per Patient" Cost is between $9,500 to $15,000, including support from NCTN grant, NCORP grant capitation, NCTN Tumor Banks, & BIQSFP.

*** Moore TJ, et al.** Variation in the estimated costs of pivotal clinical benefit trials supporting the US approval of new therapeutic agents, 2015–2017:a cross-section study, *BMJ Open* 2020;10:e038863. doi:10.1136/bmjopen-2020-038863

Proposed Budget for NCTN Budget Period (FY2025-FY2030)

Proposed % Increase by NCTN Program Components For Annual Accrual of 17,000 to 18,000 Patients

NCTN Program Component	% Increase Over Prior Period
US NCTN Ops & Stats/Data Centers - Non-Capitation	10%
Canadian Collaborating Network- Non Capitation	10%
Imaging & Radiation Oncology Core (IROC)	10%
Capitation for Sites (US & Canada) - Accrual	25% to 40%
Lead Academic Participating Sites (LAPS) - Accrual	35%
Integrated Translation Science Awards (ITSAs)	Reduction of 50%
Contract Boost plus increase of 8% over Base with 4% COLA	

Current Annual Budget & Proposed 6-Yr Grant & Contract Budget in $ Millions Total Cost

Current Annual Total Cost Budget ($ Millions)	FY2025	FY2026	FY2027	FY2028	FY2029	FY2030	Avg Annual Increase Over Prior Period
$171	$216	$216	$216	$216	$216	$216	$45

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