Summary Accrual Information & Performance on NCTN Trials

3/1/2014 to 12/31/2017

Clinical Trials and Translational Research Advisory Committee Meeting - March 7, 2018

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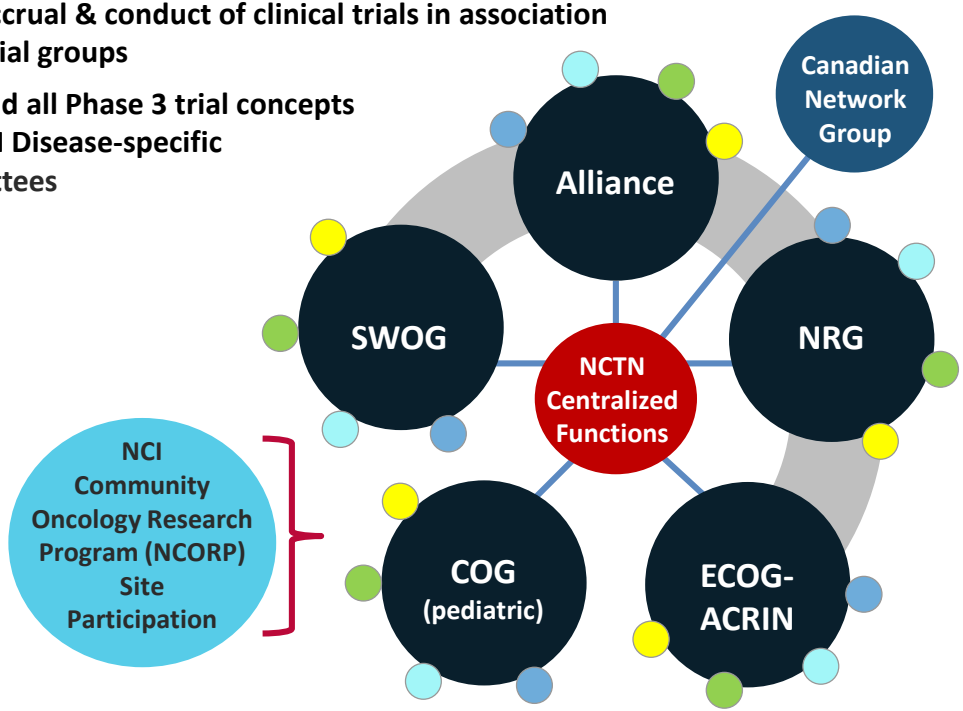
Summary Accrual Information on NCTN Trials 3/1/2014 to 12/31/2017

- NCI National Clinical Trials Network (NCTN) Structure
- Accrual & Number of Studies by Grant Year, Trial Phase, & Accrual Category
- Accrual by Geographic Distribution
- Accrual by Participating Site Category
- Accrual by Race, Gender, and Ethnicity
- Accrual by Disease Area (Adult vs Pediatric NCTN Trials)

- Accrual Performance of Phase 2/3 & Phase 3 Trials Activated Since 1-1-2014

NCI National Clinical Trials Network (NCTN) Structure

- 5 US groups (4 adult & 1 pediatric) and 1 Canadian group
- Centralized functions for operational efficiencies & integrated with NCORP
- 30 Lead Academic Participating Sites provide leadership in development, accrual & conduct of clinical trials in association with the adult trial groups
- Large Phase 2 and all Phase 3 trial concepts evaluated by NCI Disease-specific Steering Committees



LEGEND:

- Centralized Functions:
  - Centralized Institutional Review Board
  - Cancer Trials Support Unit
  - Radiotherapy/Imaging Cores
  - Common Data Management System with Central Hosting
- 30 Lead Academic Participating Sites (LAPS)
- Operations Centers
- Statistics & Data Mgt Centers
- Tumor Banks
- Member Sites

http://www.cancer.gov/clinicaltrials/nctn

NCTN Accrual by Trial Phase & Type

3/1/2014 through 12/31/2017 (46 Months)

	Grant Year 1 (3/1/2014 to 2/28/2015)			Grant Year 2 (3/1/2015 to 2/29/2016)			Grant Year 3 (3/1/2016 to 2/28/2017)			Grant Year 4 - 10 Months Only (3/1/2017 to 12/31/2017)		
NCTN Trial Phase	# Studies	Intervention & Cohort Accrual	Screening on Study Accrual	# Studies	Intervention & Cohort Accrual	Screening on Study Accrual	# Studies	Intervention & Cohort Accrual	Screening on Study Accrual	# Studies	Intervention & Cohort Accrual	Screening on Study Accrual
Phase 1	13	155	0	6	158	0	7	77	3	7	61	19
Phase 1/2	14	237	0	11	308	0	11	162	9	11	92	34
Phase 2	72	2,056	221	74	2,162	1,561	86	2,354	5,170	97	2,026	1,960
Phase 2/3	14	615	225	16	918	1,031	15	1,070	1,235	14	830	480
Phases 3	75	12,573	1,119	69	10,364	1,193	64	10,493	1,087	62	9,447	1,392
Imaging	5	243	0	4	77	0	3	46	0	0	0	0
Other	3	280	3	3	1,835	22	4	2,664	11	2	1,057	8
Pilot	3	99	0	2	41	0	1	4	0	1	23	0
TOTAL	199	16,258	1,568	185	15,863	4,200	191	16,870	7,515	194	13,536	3,893
Total # Unique Patients: 17,244				Total # Unique Patients: 18,553			Total # Unique Patients: 22,088			Total # Unique Patients: 14,651		

Total # Unique Patients for Entire 46-Month Period: 72,536 Patients

	Intervention & Cohort Accrual	Screening on Study Accrual
Est. EOY	16,243	4,671

Est. EOY Total # Unique Patients: 17,581

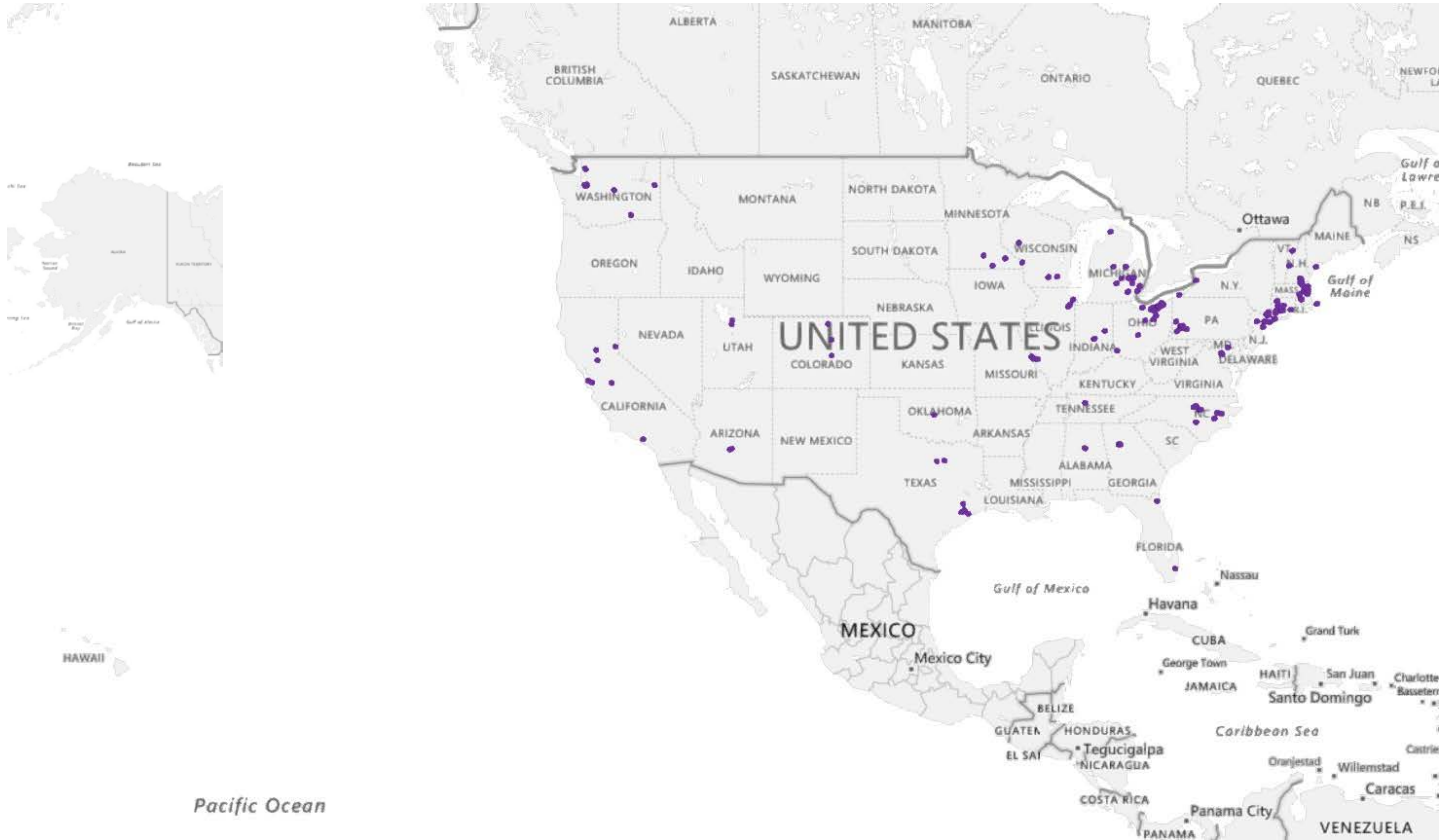
Note on the # of Studies:

1) The count for the # of studies recorded above represents the # of studies open during the reporting period that had at least 1 patient enrolled

2) The master screening and individual sub-studies of the NCTN Precision Medicine Umbrella trials (i.e., Adult MATCH, Pediatric MATCH, and LUNG-MAP) are counted as separate individual studies

Participating Sites with at Least 1 Patient Enrolled to NCTN Studies between March 1, 2014 and December 31, 2017

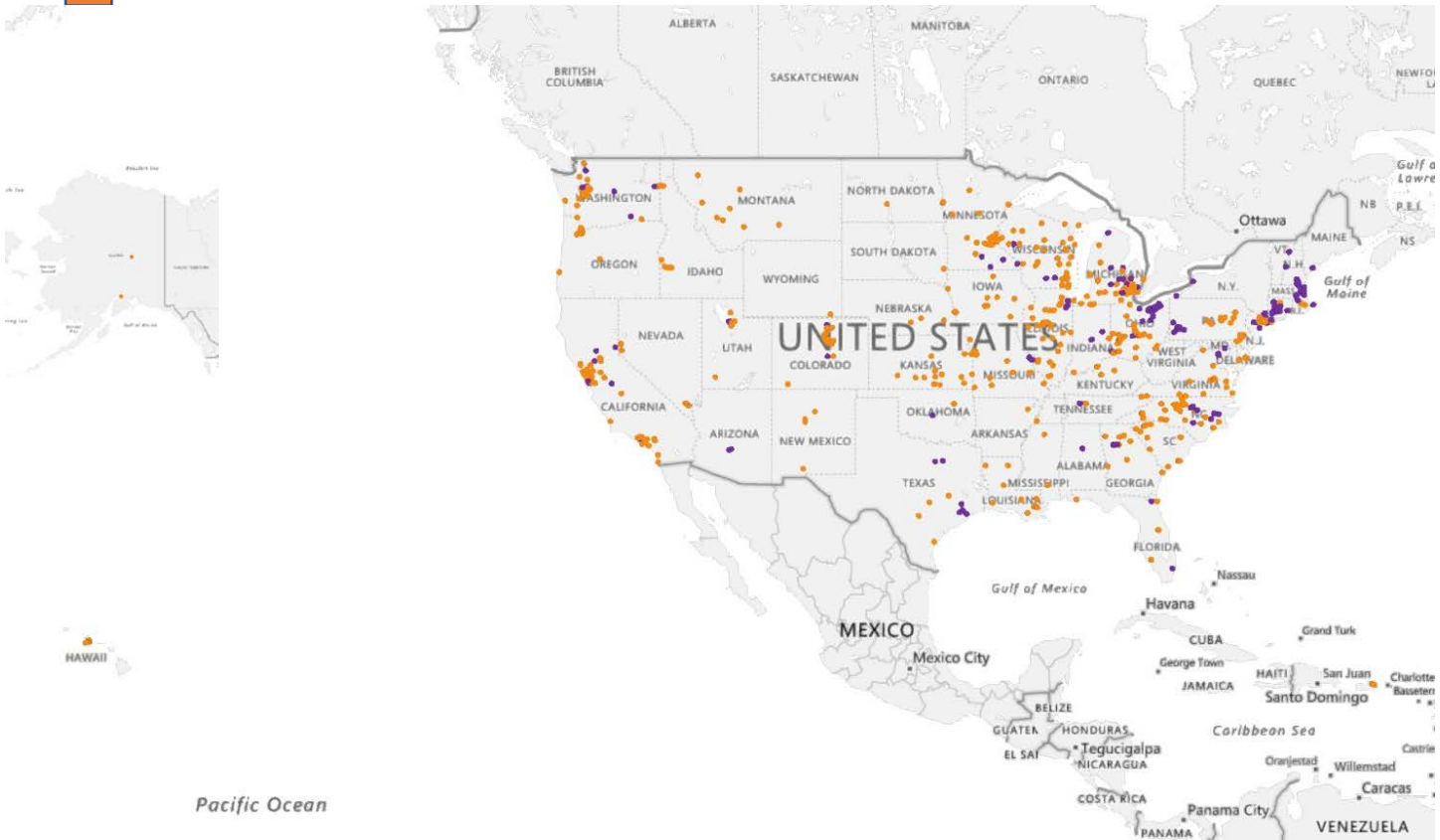
NCTN LAPS sites



Participating Sites with at Least 1 Patient Enrolled to NCTN Studies between March 1, 2014 and December 31, 2017

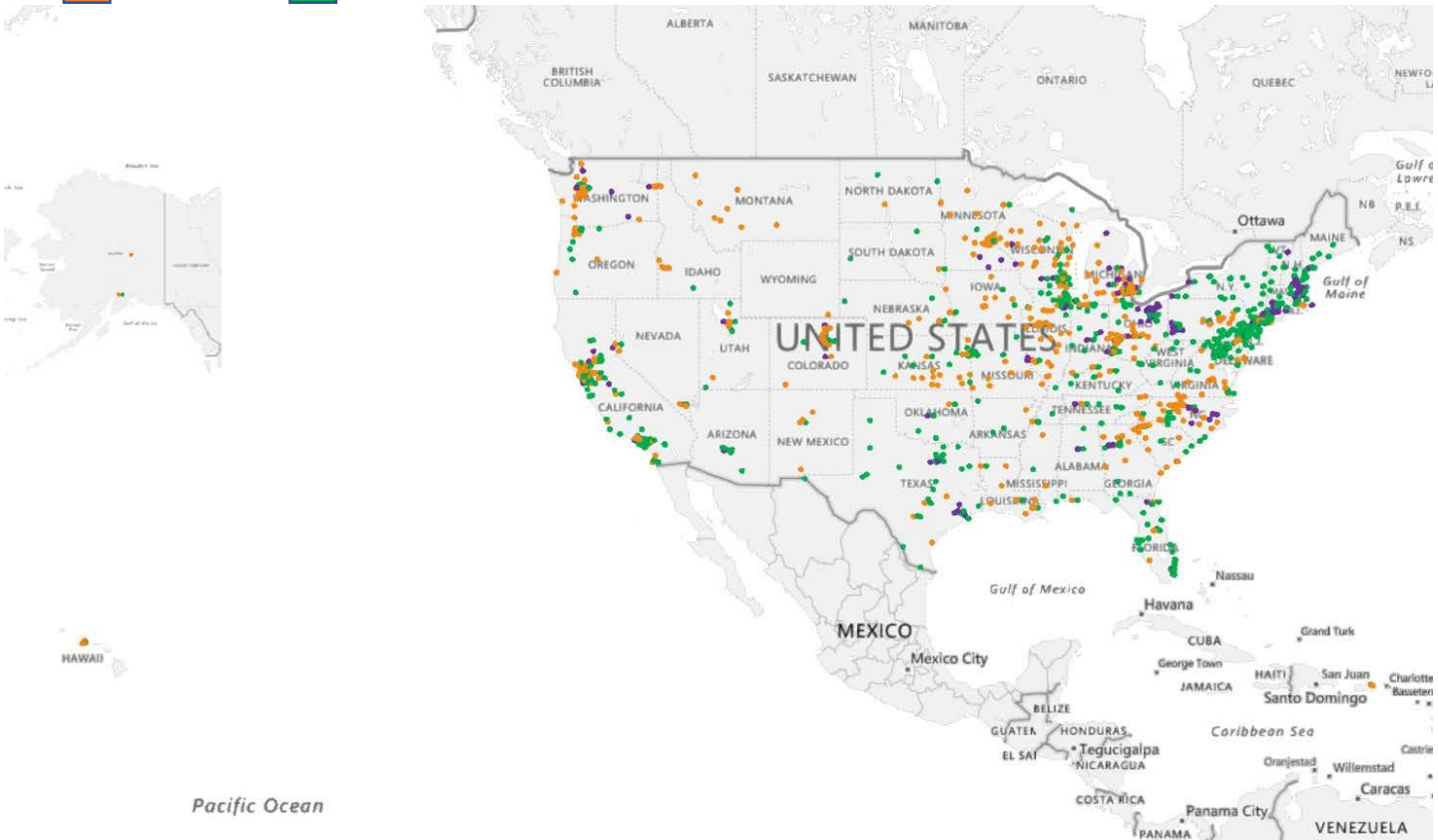
NCTN LAPS sites

NCORP Sites



Participating Sites with at Least 1 Patient Enrolled to NCTN Studies between March 1, 2014 and December 31, 2017

NCTN LAPS sites | NCORP Sites | NCTN US Full Member Sites



Participating Sites with at Least 1 Patient Enrolled to NCTN Studies between March 1, 2014 and December 31, 2017

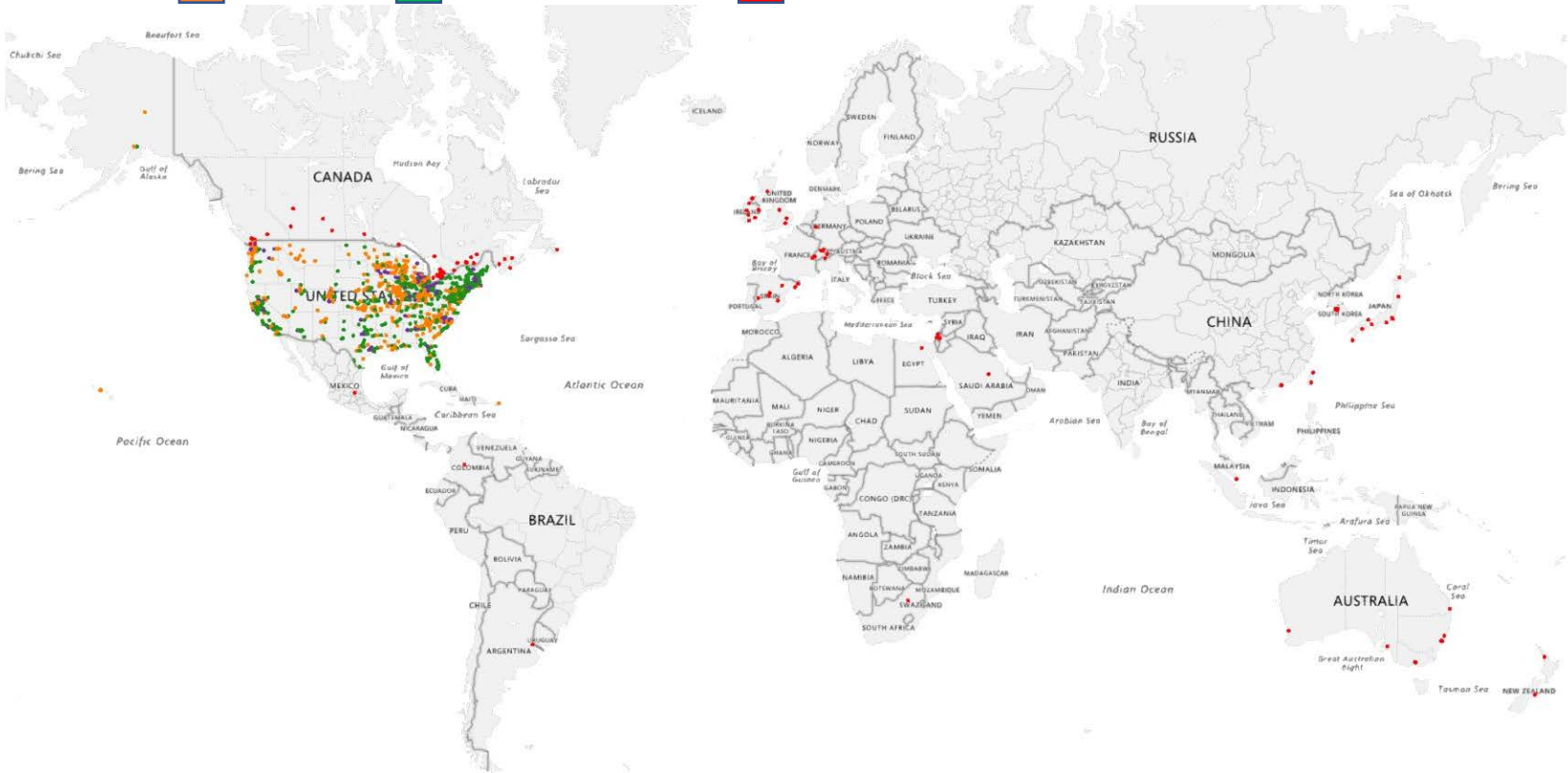
NCTN LAPS sites

NCOPR Sites

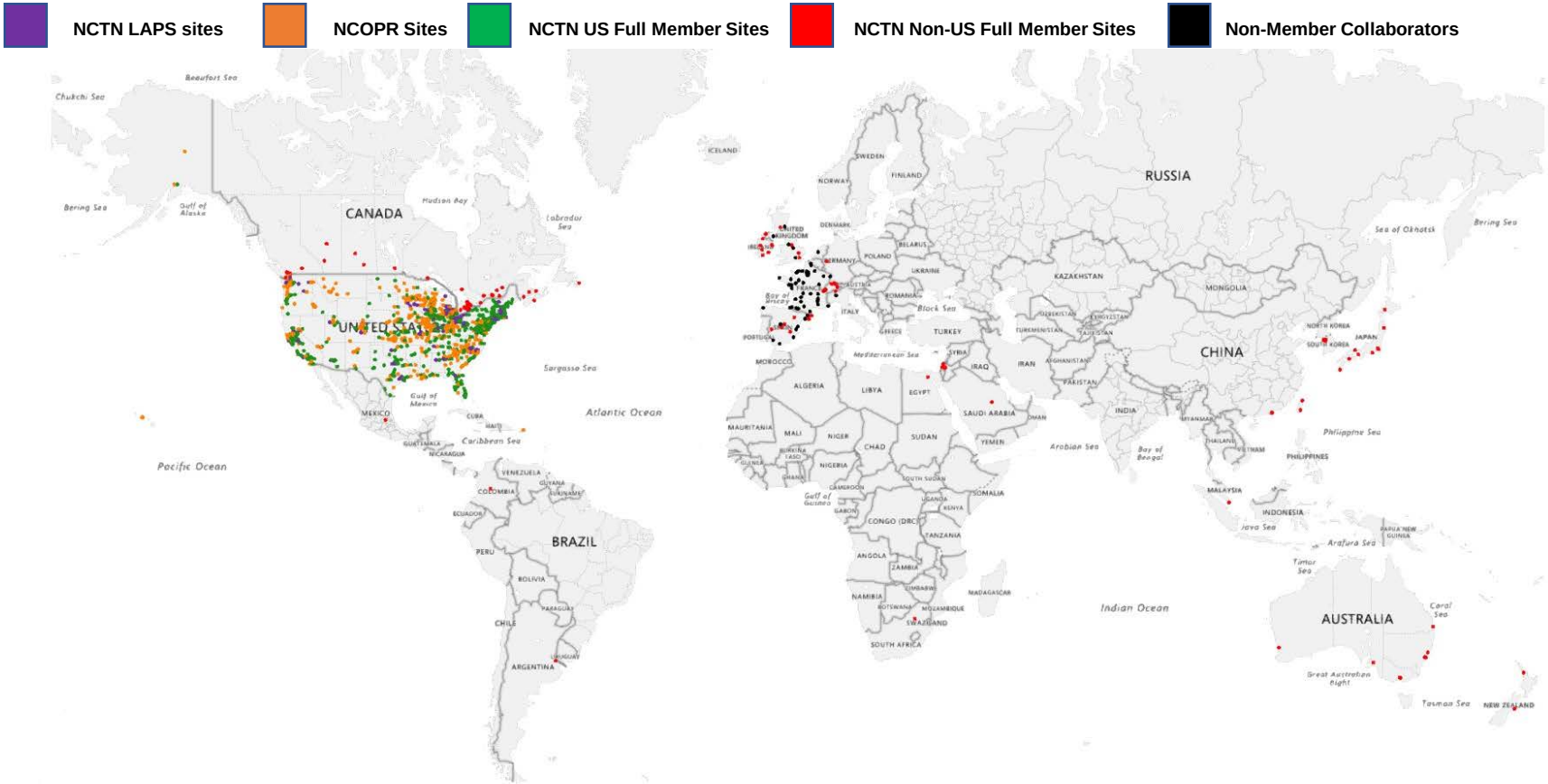
NCTN US Full Member Sites

Participating Sites with at Least 1 Patient Enrolled to NCTN Studies between March 1, 2014 and December 31, 2017

NCTN LAPS sites | NCOPR Sites | NCTN US Full Member Sites | NCTN Non-US Full Member Sites



Participating Sites with at Least 1 Patient Enrolled to NCTN Studies between March 1, 2014 and December 31, 2017



NCTN Accrual by Participating Site Category

3/1/2014 through 12/31/2017 (46 Months)

Unique Number of Patients Enrolled on NCTN Trials (*) from 3/1/2014 to 12/31/2017				
Site Category	# Sites	% Total Sites	Accrual	% Total Accrual
LAPS (US)	163	9%	15,890	22%
NCORP (US)	625	35%	20,016	28%
Rostered (US)	770	43%	29,993	41%
Sub-Total US	1,558	87%	65,899	91%
Full Members of NCTN Groups (Ex-US) including Canadian Clinical Trials Group				
Canadian	68	4%	2,991	4%
Non- Canadian	98	5%	1,894	3%
Non- Member Collaborators (Ex-US)	70	4%	1,752	2%
Total Sites	1,794	100%	72,536	100%

LAPS: US Lead Academic Participating Sites

NCORP: US NCI Community Oncology Research Program

Rostered: All Other US Sites

(*) Unique # of patients are those patients who were "Screened on Study" and/or underwent the "Study Intervention"

NCTN Accrual by Race, Gender, & Ethnicity

3/1/2014 through 12/31/2017 (46 Months) – All Enrolled Patients

Racial Categories	Ethnic Categories									Total - All Countries	% of All Reported Racial Categories)
	Not Hispanic or Latino			Hispanic or Latino			Unknown/ Not Reported Ethnicity				
	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported	Female	Male	Unknown/ Not Reported		
American Indian/ Alaska Native	210	135	0	62	39	0	10	4	0	460	1%
Asian	1,815	1,071	0	16	14	0	31	56	0	3,003	4%
Native Hawaiian or Other Pacific Islander	128	94	0	9	10	0	3	1	0	245	0.4%
Black or African American	3,560	2,446	0	92	43	0	93	53	0	6,287	9%
White	26,971	23,332	1	2,985	2,263	0	638	567	0	56,757	85%
More than One Race	105	78	0	24	12	0	2	3	0	224	0.3%
TOTAL (All Reported Racial Categories)	32,789	27,156	1	3,188	2,381	0	777	684	0	66,976	100%
Unknown or Not Reported	623	653	0	907	724	0	1,967	641	45	5,560	8% of All Pts Enrolled with Unknown/Not Reported Race
Total	33,412	27,809	1	4,095	3,105	0	2,744	1,325	45	72,536	

NCTN Accrual by Race, Gender, & Ethnicity

3/1/2014 through 12/31/2017 (46 Months) – All Enrolled Patients

(Demographic Data Not Adjusted Based on Types of Cancer Under Study in the Trials)

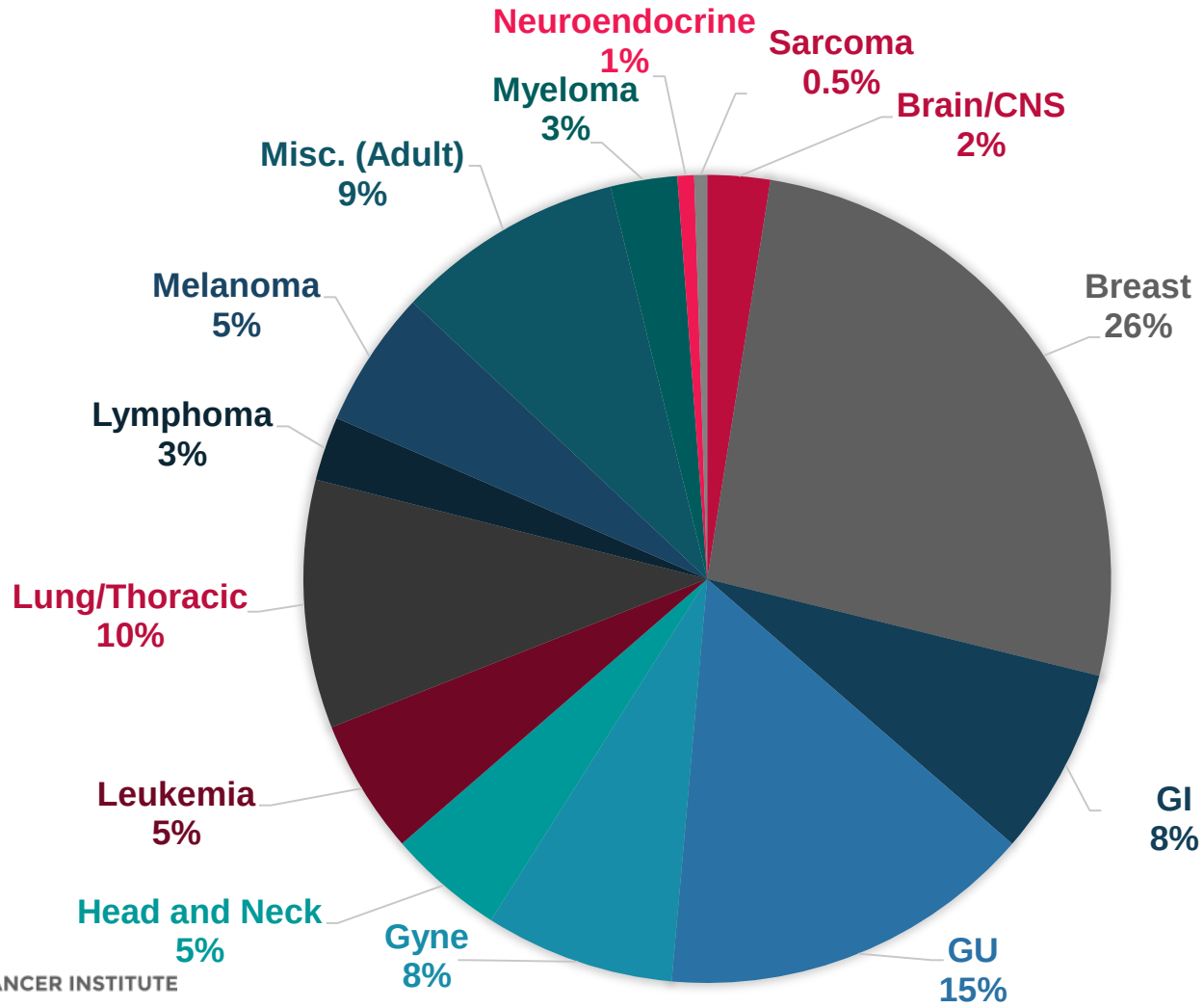
All Racial Minorities as % of All Patients Reporting Race:	**15%**
More than One Race as % of All Patients Reporting Race:	**0.3%**
Hispanic or Latino as % of All Patients Reporting Ethnicity:	**9%**
Patients Not Reporting Ethnicity as % of All Enrolled Patients:	**4%**
% White and Non-Hispanic/Latino Ethnicity:	**69%**
% Non-White and/or Hispanic Ethnicity:	**24%**
% Patient Not Reporting Race and Ethnicity or White and Not Reporting Ethnicity or Not Hispanic/Latino and Not Reporting Race:	**7%**

NCTN Accrual by Race, Gender, & Ethnicity

3/1/2014 through 12/31/2017 (46 Months) – All Enrolled Patients

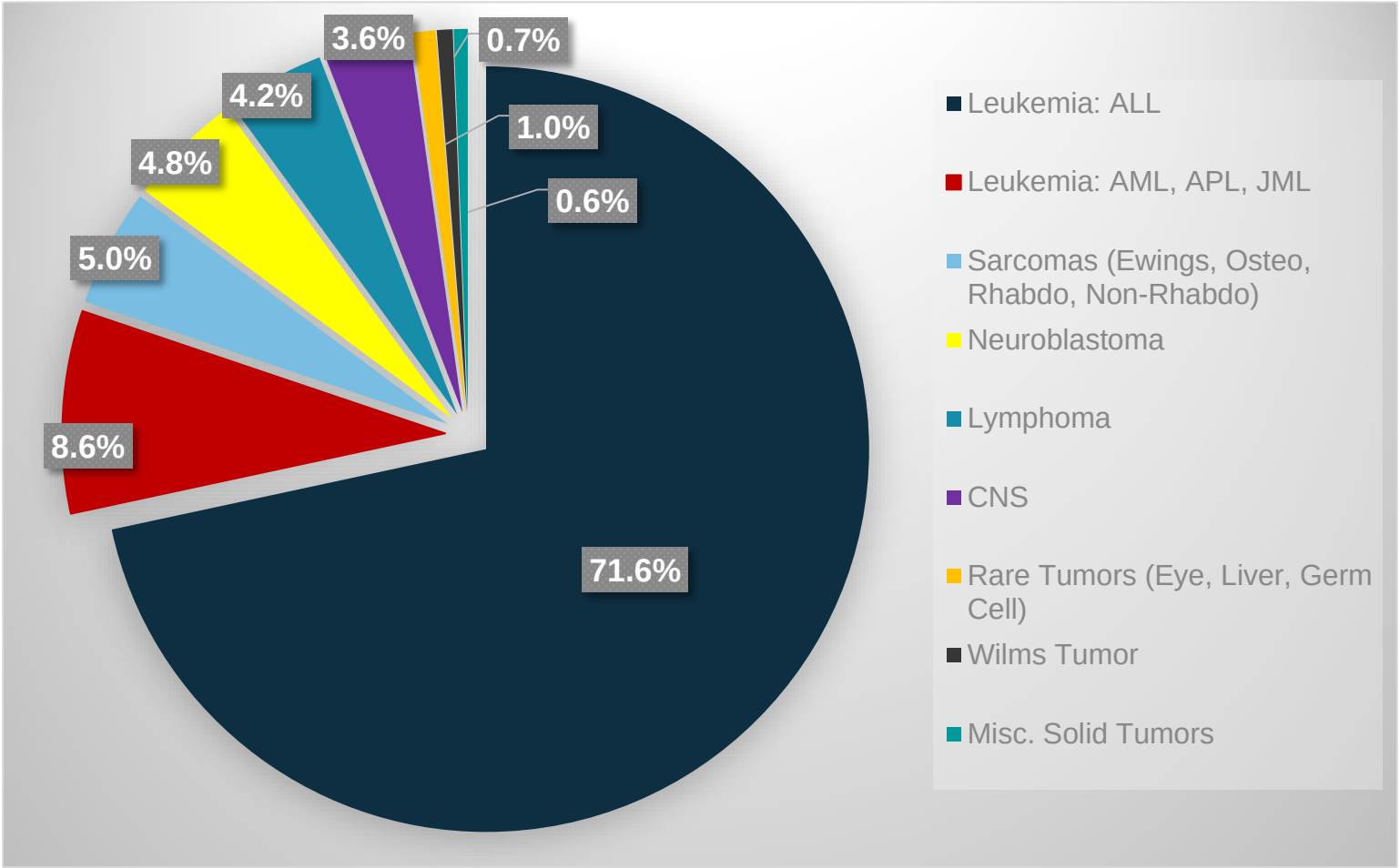
(Demographic Data Not Adjusted Based on Types of Cancer Under Study in the Trials)

% Female of All Patients Reporting Gender:	**56%**
% Male of All Patients Reporting Gender:	**44%**
% Patients Not Reporting Gender of All Patients Enrolled:	**0.1%**



Intervention & Cohort Accrual on ADULT NCTN Studies by Major Disease Area

3/1/2014 through 12/31/2017



Intervention & Cohort Accrual on PEDIATRIC NCTN Studies by Major Disease Area

3/1/2014 through 12/31/2017

Accrual Performance of NCTN Phase 2/3 and 3 Trials Activated Since 1-1-2014

Development of Early Stopping Guidelines for Slow Accruing NCTN Phase 2/3 & Phase 3 Treatment Trials

- The guidelines were initially developed in 2005 on a database of 239 phase 3 trials in the former NCI-sponsored Cooperative Group Program initiated on or prior to 2000 that stayed open for >15 months. This data base was then randomly split into a training subset & a validation subset.

- Early accrual feasibility was measured in terms of the fraction of projected accrual in quarters 5-6. Overall trial success was judged by whether final trial accrual was over 80% to 90% of projected.

- Based on analysis of the early accrual rates, the cut-off of <20% of projected accrual in Quarters 5-6 was selected for termination of a study and the cut-off of 50% of projected accrual in Quarter 8 was selected to allow the trial to continue without formal re-assessment of feasibility by CTEP based on the guidelines; the DSMBs overseeing the trials continue to assess accrual.

CTEP Slow Accrual Guidelines for NCTN Phase 2/3 and Phase 3 Treatment Trials

The Guidelines developed in 2005 were applied to phase 3 trials activated after April 1, 2004 and extended to phase 2/3 trials at the start of the NCTN in 2014. Accrual is monitored carefully after activation to identify accrual issues early & intervene as soon as possible to improve accrual; however, the formal time points for assessment are:

If the accrual in Quarter 5-6 is:

≤ 20% of projected accrual rate → STOP trial

< 50% and > 20% of projected accrual rate → Study Team given 6 months to improve accrual

If the accrual in Quarter 8 is:

< 50% of projected accrual rate → Trial may be amended to reflect actual accrual with approval of amendment based on implications of this new rate on study relevance and feasibility

Previous CTEP Analyses of Accrual for the NCI-Sponsored Cooperative Group Phase 3 Trials

Primary Reasons for <90% Accrual:

- Interim Monitoring
- External Information
- Drug Supply Issues
- Unacceptable Toxicity
- Achieved Sufficient # of Events
- Inadequate Accrual Rate

	All Phase 3 Trials	
	Years Trials Activated	
	2000 - 2010	2000 - 2007
# All Trials Activated During this Time Period	254	191
# Trials with <90% Projected Total Accrual Due to Inadequate Accrual Rates	21.1%	22.0%
% Patients on Trials with <90% Projected Accrual (Due to Inadequate Accrual Rates) Out of All Patients Enrolled on Trials Activated During this Time Period	1.6%	1.7%

Major Reasons for Inadequate Accrual Rates Identified in Previous Analyses

- **Challenging Randomization (+/- Modalities):**
  - ❑ **Observation vs Chemotx**
  - ❑ **Observation vs Early Intervention**
  - ❑ **Surgery vs RT; +/- Transplant, +/- RT; Chemotx vs ChemoRT**
  - ❑ **Neoadjuvant vs Adjuvant Therapy**
- **Site Interest in Treatment Approach Not Sufficiently High**
- **Competing Studies**
- **Rare Cancers**

Analysis of NCTN Phase 2/3 & Phase 3 Treatment Trials by Slow Accruing Guidelines

Period of Activation: January 1, 2014 through December 31, 2017

Period of Accrual: January 1, 2014 through March 2, 2018

Trial Phase	# Total Trials Activated	# Total Trials with Qtr 5-6 Accrual	# Trials with Qtr 4 Accrual	# Trials with <9 Months Accrual
Phase 2/3 (*)	14	9	2	4
Phase 3	41	25	3	12
Total	55	34	5 (**)	16

(*) Excludes 5 LUNG-MAP sub-protocols changed from Phase 2/3 to Phase 2 Trials

(**) All these trials are already between 31% and 70% of their accrual rates at Quarter 4

Analysis of NCTN Accrual for Phase 2/3 Trials by Slow Accruing Guidelines (continued)

Trial Phase	# Total Trials with Qtr 5-6 Accrual	# Trials ≤ 20% of Projected Rate	# Trials >20% and <50% of Projected Rate (*)	# Trials > 50% of Projected Rate	Estimated % of "At Risk Trials" Currently (i.e., May Not Reach 80-90% of Target)
2/3	9	0	3	6	22% (2/9)

(*) Of these 3 trials, 2 had accrual rates <50% at Quarter 8 indicating that they may not reach 80% to 90% of their target accruals. Reasons for low accrual are described below for the trials:

- Nasopharyngeal cancer trial that required international site participation and required molecular testing in country – international participation has now been arranged with appropriate support.
- NSCLC cancer trial appears that it will eventually met its phase 2 accrual goal, but not sufficient interest at participating sites to reach the phase 3 accrual goal.

Analysis of NCTN Accrual for Phase 3 Trials by Slow Accruing Guidelines (continued)

Trial Phase	# Total Trials with Qtr 5-6 Accrual	# Trials ≤ 20% of Projected Rate (**)	# Trials >20% and <50% of Projected Rate	# Trials > 50% of Projected Rate	Estimated % of "At Risk Trials" Currently (i.e., May Not Get to 80-90% of Target)
3	25 (*)	3	5	17	12% (3/25)

(*) A phase 3 trial was removed from this category since it trial had a safety-run that required a long evaluation period. It opened to its phase 3 component on 7/20/2017 and has <9 months of accrual history.

(**) These 3 trials may not may not reach 80% to 90% of their target accruals. The trials are in rare tumors/rare molecular sub-sets of tumors (cholangiocarcinoma, solitary plasmacytoma, & ALK + NSCLC in adjuvant setting.

Example: Accrual Rates to the ALCHEMIST Tx Trials

ALCHEMIST Screening/Cohort Trial - A151216
Accrual: 2,887 as of 3/2/2018
Target Screening: 6,000 to 8,000

Non-Squamous

E4512: Open 8/18/2014
ALK +
Crizotinib *vs* Observation after standard adj tx

Qtr 1-3 Accrual Rate: 2%
Qtr 5-6 Accrual Rate: 17%
Qtr 8 Accrual Rate: 17%

Accrual: 59
Target: 378

Projected accrual at time EGFR trial completes based on current rate: ~200

A081105: Open 8/18/2014
EGFR Mutation +
Erlotinib *vs* Observation after standard adj tx

Qtr 1-3 Accrual Rate: 8%
Qtr 5-6 Accrual Rate: 42%
Qtr 8 Accrual Rate: 40%

Accrual: 180
Target: 450

Projected time to complete based on current rate: 3.5 Yrs

Squamous & Non-Squamous

EA5142: Open 5/26/2016
PD-L1 Stratification
Nivolumab *vs* Observation after standard adj tx

Qtr 1-3 Accrual Rate: 29%
Qtr 5-6 Accrual Rate: 90%
Qtr 8 Accrual Rate: N/A

Accrual: 306
Target: 714

Projected time to complete based on current rate: 1.5 Yrs

Example: Accrual Rates for the 5 Completed Tx Trials

Trial #	Trial Title	Study Phase	Activation Date (Closure Date)	Target Accrual	Accrual as % of the Planned Accrual Rate			
					Qtr 1-3	Qtr 4	Qtr 5-6	Qtr 8
A031201	A Phase III Trial of Enzalutamide vs Enzalutamide, Abiraterone and Prednisone for Castration Resistant Metastatic Prostate Cancer	3	1/22/2014 (8/13/2016)	1224	222 (73%)	78 (76%)	244 (120%)	137 (134%)
GOG-0281	A Randomized Phase II/III Study to Assess the Efficacy of Trametinib in Patients with Recurrent or Progressive Low-Grade Serous Ovarian Cancer or Peritoneal Cancer	2/3	2/27/2014 (Scheduled on 4/10/2018)	250	23 (43%)	16 (89%)	40 (111%)	10 (56%)
GOG-0286B	A Randomized Phase II/III Study of Paclitaxel/Carboplatin/Metformin vs Paclitaxel/Carboplatin/Placebo as Initial Therapy for Measurable Stage III or IVA, Stage IVB, or Recurrent Endometrial Cancer	2/3	3/17/2014 (2/1/2018)	540	95 (81%)	59 (151%)	130 (167%)	52 (133%)
A091105	A Phase III, Double Blind, Randomized, Placebo-Controlled Trial of Sorafenib in Desmoid Tumors or Aggressive Fibromatosis (DT/DF)	3	3/21/2014 (12/1/2016)	83	11 (31%)	11 (92%)	39 (163%)	Trial Closed Before End Qtr 8
S1404	A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to Pembrolizumab in Patients with High Risk Resected Melanoma	3	10/15/2015 (8/16/2017)	1378	228 (56%)	190 (119%)	513 (190%)	Trial Closed Before End Qtr 8

Example: Accrual Challenges for Trials After Activation

Trial #	Trial Title	Study Phase	Activation Date (Closure Date)	Target Accrual	Accrual as % of Planned Accrual Rate			
					Qtr 1-3	Qtr 4	Qtr 5-6	Qtr 8
A031102	Randomized Phase 3 Trial Comparing Conventional-Dose Chemotx Using Paclitaxel, Ifosfamide, and Cisplatin (TIP) with High-Dose Chemotx Using Mobilizing Paclitaxel Plus Ifosfamide Followed by High-Dose Carboplatin & Etoposide (TI-CE) as 1st Salvage Tx in Relapsed or Refractory Germ Cell Tumors	3	7/1/2015	420	8 (11%)	9 (38%)	17 (35%)	14 (58%)
EA6134	Randomized Phase 3 Trial of Dabrafenib + Trametinib Followed by Ipilimumab + Nivolumab at Progression vs. Ipilimumab + Nivolumab Followed by Dabrafenib + Trametinib at Progression in Patients with Advanced BRAFV600 Mutant Melanoma	3	7/13/2015	300	35 (24%)	9 (19%)	26 (27%)	21 (44%)

A031102: Challenges related to delays in bringing in international sites (non-member collaborators)

EA6134: Challenges related to interruption in drug supply in Quarter 4

Summary of Accrual Performance on Initial NCTN Phase 2/3 and Phase 3 Trials Activated

- The rate of “At Risk Trials” for closure due to poor accrual appears to be in the range of 12% to 22%
- The “At Risk Trials” do not perform well right from the beginning of trial activation
- Most “At Risk Trials” were in rarer tumor types (or rare molecular sub-sets of common tumors) and were aggravated by other factors (e.g., clinical setting, specialized focus, referral patterns, need for international site participation)
- Estimating % of patients with specific molecular sub-sets of disease is challenging with respect to planning accrual time-frames (e.g., LUNG-MAP, ALCHEMIST) especially if there are other factors in the trial that may impede accrual.
- Even with the challenging, many rare tumor trials do accrue well with careful planning and commitment (e.g., desmoid tumor trial, low-grade serous ovarian cancer)

On-Going Activities in Monitoring Accrual to NCTN Phase 2/3 and Phase 3 Trials

- Accrual Intervention projects for trials identified as potentially challenging with respect to accrual
- Enhancement of “feasibility” assessment for trials at concept development and during concept evaluation & improved monitoring of trials as well as improved projections for trials
- Expanding eligibility criteria whenever possible
- Continued evaluation of why trials succeed or fail due to accrual issues