Friends Annual Meeting

Supported by:

American Association for Cancer Research
American Society of Clinical Oncology
Susan G. Komen

FRIENDS of CANCER RESEARCH

FRIENDS ANNUAL MEETING

KEYNOTE CONVERSATION

Robert Califf, MD; FDA Commissioner

Doug Lowy, MD; NCI Acting Director

Ellen V. Sigal, PhD; Chair & Founder, *Friends*

FRIENDS of CANCER RESEARCH

FRIENDS ANNUAL MEETING

PANEL ONE:
MODERNIZATION OF ELIGIBILITY CRITERIA

FRIENDS of CANCER RESEARCH

FRIENDS ANNUAL MEETING

EDWARD KIM, MD, FACP

LEVINE CANCER INSTITUTE

CAROLINAS HEALTHCARE SYSTEM

Panelists

- **Edward Kim, MD**; Levine Cancer Institute, Carolinas Healthcare System
- **Paul Hesketh, MD**; Lahey Health Cancer Institute
- **Pratik Multani, MD**; Ignyta
- **Rajeshwari Sridhara**, PhD; FDA
- **Nancy Roach**; Fight Colorectal Cancer
- **Gwynn Ison, MD**; FDA
- **Eric Rubin, MD**; Merck
- **Andrea Denicoff, RN**; NCI
- **Elizabeth Garrett-Mayer, PhD**; Medical University of South Carolina

ASCO-Friends of Cancer Research Modernizing Eligibility Criteria Project

Edward S. Kim, MD, FACP

Chair, Solid Tumor Oncology and Investigational Therapeutics

Donald S. Kim Distinguished Chair for Cancer Research

Levine Cancer Institute, Carolinas HealthCare System

Charlotte, North Carolina

Panel Overview

- Provide high-level overview of ASCO-Friends project
  - Working Group recommendations and implementation considerations
- Discuss efforts to address accrual challenges after trial implementation
- Identify practical examples of trials with broader eligibility criteria
- Discuss potential trial designs for including broad patient populations in trials & how different approaches might impact the drug label
- Incorporate patient considerations

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SPECIAL ARTICLE

Modernizing Eligibility Criteria for Molecularly Driven Trials

Edward S. Kim, David Bernstein, Susan G. Hilsenbeck, Christine H. Chung, Adam P. Dicker, Jennifer L. Ersek, Steven Stein, Fadlo R. Khuri, Earle Burgess, Kelly Hunt, Percy Ivy, Suanna S. Bruinooge, Neal Meropol, and Richard L. Schilsky

Edward S. Kim, Jennifer L. Ersek, and Earle Burgess, Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC; David Bernstein, Suanna S. Bruinooge, and Richard L. Schilsky, American Society of Clinical Oncology, Alexandria, VA; Susan G. Hilsenbeck, Dan L. Duncan Cancer Center, Baylor College of Medicine; Kelly Hunt, University of Texas MD Anderson Cancer Center, Houston, TX; Christine H. Chung, Johns Hopkins University School of Medicine, Baltimore; Percy Ivy, National Cancer Institute, Bethesda, MD; Adam P. Dicker, Sidney Kimmel Medical College and Cancer Center at Thomas Jefferson University, Philadelphia, PA; Steven Stein,

ABSTRACT

As more clinical trials of molecularly targeted agents evolve, the number of eligibility criteria seems to be increasing. The importance and utility of eligibility criteria must be considered in the context of the fundamental goal of a clinical trial: to understand the risks and benefits of a treatment in the intended-use patient population. Although eligibility criteria are necessary to define the population under study and conduct trials safely, excessive requirements may severely restrict the population available for study, and often, this population is not reflective of the general population for which the drug would be prescribed. The American Society of Clinical Oncology Cancer Research Committee, which comprises academic faculty, industry representatives, and patient advocates, evaluated this issue. Evaluation results were mixed. Most physicians agreed that excessive eligibility criterias slow study enrollment rates and prolong the duration of enrollment; however, this hypothesis was difficult to validate with the data examined. We propose the organization of a public workshop, with input from regulatory bodies and key stakeholders, with the goal of developing an algorithmic approach to

Recommended Approach to Eligibility Criteria Consideration

Category	Question for Consideration
Relationship to scientific objective	Does the eligibility criterion support the scientific hypothesis?
	Could the scientific goal be achieved without including this particular eligibility criterion?
Generalizability	Will the results of the study be applicable to a patient not enrolled on the study?
	Are the eligibility criteria too restrictive for practical clinical use?
Patient safety and drug toxicity	Is patient safety being adequately protected and does this eligibility criterion contribute to this?
	Are potential drug toxicities and mechanism of action being accounted for and does limiting or including this criterion support or hinder the scientific goal?
Continual review on a regular basis	At what point should eligibility criteria be re-justified during protocol development and during enrollment?
	Should a trial close due to poor accrual or be allowed to reduce/relax eligibility criteria as a first step?

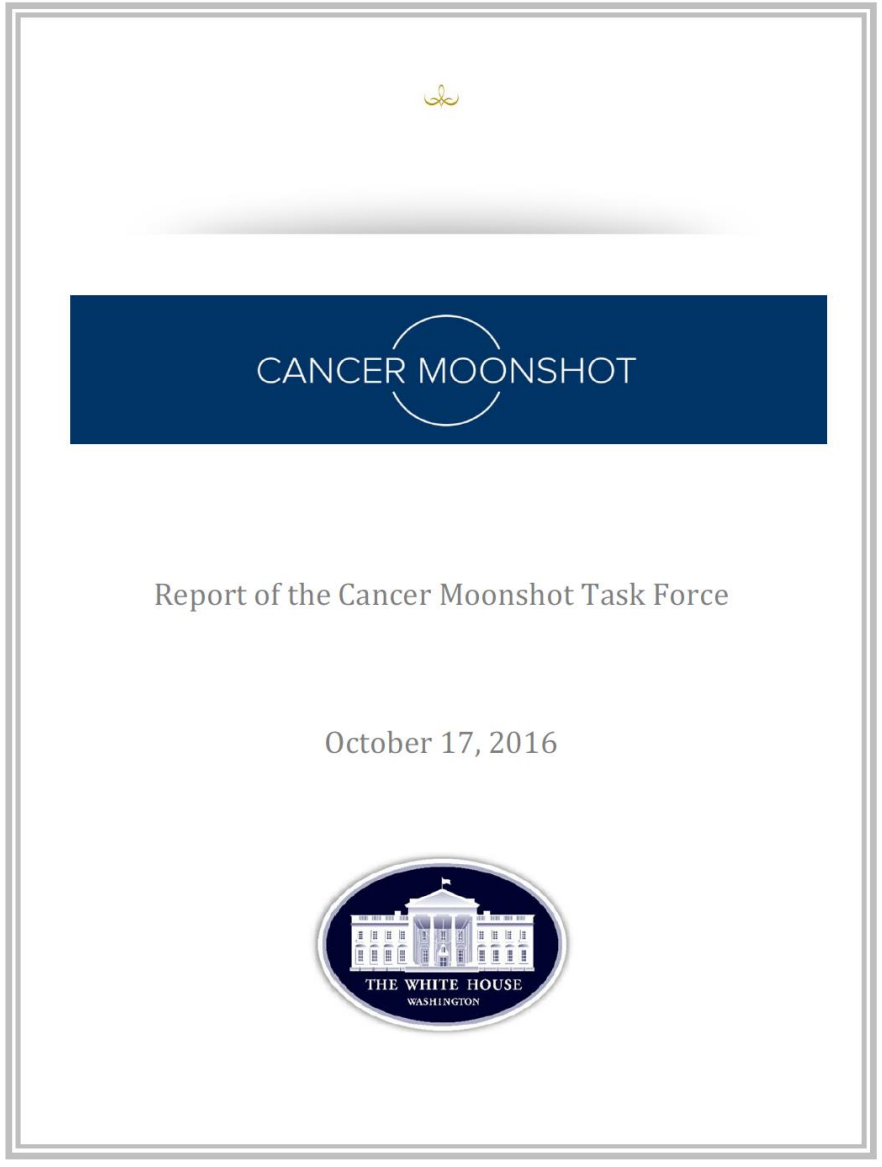
Kim ES. ASCO 2016

Importance to Cancer Moonshot

Strategic Goal 3– Accelerate Bringing New Therapies to Patients: Plans for Year 2 & Beyond

1. **Modernize eligibility criteria for clinical trials**

   "In coordination with the American Society of Clinical Oncology, Friends of Cancer Research, and other stakeholders, FDA will evaluate clinical trial entrance criteria that may unnecessarily restrict clinical trial access—such as brain metastases, HIV status, organ dysfunction, and age restrictions (e.g., pediatrics)—to better assess when restrictions are warranted for specific clinical trials to protect patient safety. … Moving forward, FDA will work with sponsors to improve the use of science-based, clinically relevant eligibility criteria to allow greater patient access to clinical trials while maintaining patient safety."



What is the goal?

- Challenge assumptions & past practice
- Create new culture – only exclude where safety warrants
  - Shape the perception/attitudes/practice of clinical trial eligibility
  - Create new language to use
  - Active discussion during trial design & FDA pre-IND meetings to justify exclusions or differences between trial participants and overall patient population with the indicated disease
- Not just publication of recommendations, but implementation

ASCO-Friends Project Overview

- Prioritized assessment of four eligibility criteria
  - Brain Metastases; Minimum Age; HIV/AIDS; & Organ Dysfunction, Prior Malignancies, and Comorbidities
- Formed multi-stakeholder working groups
  - Patient advocates
  - Clinical investigators
  - FDA medical reviewers
  - Drug and biotech manufacturers
  - NCI
  - Biostatisticians
  - Pharmacologists

ASCO-Friends Project Leadership

ASCO
Edward S. Kim, MD, FACP
Richard L. Schilsky, MD, FACP, FASCO
Suanna Bruinooge, MPH
Caroline Schenkel, MSc

FDA
Richard Pazdur, MD
Gwynn Ison, MD
Julia Beaver, MD
Tatiana Prowell, MD
Raji Sridhara, PhD

Working Group Chairs
Stuart Lichtman, MD (MSKCC)
Nancy Lin, MD (Harvard & RANO Group)
Thomas Uldrick, MD (NCI)
Lia Gore, MD (Univ. of CO)

Friends of Cancer Research
Ellen Sigal, PhD
Jeff Allen, PhD
Samantha Roberts, PhD
Marina Kozak, PhD

Planning Committee
Eric Rubin, MD (Merck)
Nancy Roach (Fight Colorectal Cancer)
Elizabeth Garret-Mayer (Medical Univ. of SC)

Brain Metastases WG Recommendations

- Patients with treated or stable brain metastases:
  - Routinely include in all phases, except where compelling rationale for exclusion.
- Patients with new/active/progressive brain metastases:
  - A one-size-fits-all approach is not appropriate. Factors such as history of the disease, trial phase and design, and the drug mechanism and potential for CNS interaction should determine eligibility.
- Patients with leptomeningeal disease:
  - In most trials, it remains appropriate to exclude patients with leptomeningeal disease, although there may be situations that warrant a cohort of such patients in early phase trials.

Minimum Age WG Recommendations

- Initial dose-finding trials:
  - Pediatric-specific cohorts should be included when there is strong scientific rationale (based on molecular pathways or histology and preclinical data)

- Later-phase trials:
  - Trials in diseases that span adult and pediatric populations should include pediatric patients with the specific disease under study
  - Patients aged 12 years and above should be enrolled in such trials

HIV/AIDS WG Recommendations

- HIV-related eligibility criteria should straight-forward and focus on:
  - Current and past CD4 and T-cell counts
  - History (if any) of AIDS-defining conditions such as opportunistic infections other than historically low CD4 and T-cell counts
  - Status of HIV treatment

- Healthy HIV-positive patients that are included in cancer clinical trials should be treated using the same standards as other patients with co-morbidities, and anti-retroviral therapy should be considered a concomitant medication.

Organ Dysfunction, Prior Malignancies, and Comorbidities WG Recommendations

- WG recommendations were informed by analysis of dataset of 13,000 patients newly diagnosed in 2013-2014.
  - WG prioritized renal function criteria most often excluded patients from trials.
  - Additional analysis should inform recommendations on hepatic or cardiac function.

- Renal function should be based on creatinine clearance (calculated using the Cockcroft-Gault formula) rather than serum creatinine levels.

- Liberal creatinine clearance eligibility criteria should be applied when renal excretion is not a significant component of a drug's pharmacokinetics or when known dose medication strategies allow for safe and effective administration.

Organ Dysfunction, Prior Malignancies, and Comorbidities WG Recommendations (cont.)

- Exclusions based on prior history of cancer is common.
- Exclusions based on prior malignancy should be liberalized.
- WG still discussing specific recommendations and considering:
  - Cancer types
  - If previous therapies were curative
  - If cancer not cured, but stable
  - Time lapse between previous therapy and trial

Next Steps

- Publish findings
  - Working group manuscripts & ASCO-Friends Statement – Spring 2017
- Promote implementation
  - Creating standards for EC language that is inclusive
  - Working with trial sponsors to embed recommendations
  - Developing metrics to track implementation
  - Documenting results where recommendations are used
  - Addressing practical issues that may arise
- Examine additional eligibility criteria
  - Drug washout periods
  - Concomitant medications
  - Other triggers for exclusion of elderly patients

Targeted Agent and Profiling Utilization Registry (TAPUR) Study

- Pragmatic phase 2 study with FDA-approved, targeted agents
- Incorporates general and drug-specific eligibility criteria
- Prior Malignancy:
  - No exclusion or time limit for patients with prior malignancies
- HIV+
  - General Criteria – included except where clinician decides to exclude
  - Drug-specific – pembrolizumab and olaparib exclude
- Performance Status (PS):
  - General eligibility: 0-2 per general eligibility
  - Drug-specific: pembrolizumab or regorafenib must have PS 0-1

TAPUR Study Eligibility Criteria (cont'd)

- Brain Metastases – eligible, so long as the patient is:
  - Not progressive and not on treatment
  - Has not experienced a seizure or had a clinically significant change in neurological status within the 3 months
  - Off steroids for at least one month prior to enrollment.
- Patients must have acceptable organ function as defined below:
  - AST (SGOT) and ALT(SGPT) **< 2.5 x institutional ULN (or < 5 x ULN** in patients with known hepatic metastases)
  - Serum creatinine ≤ 1.5 × ULN or **calculated or measured creatinine clearance ≥ 50 mL/min/1.73 m²**
- Pediatric Population:
  - Current TAPUR study eligibility criteria requires ≥ 18 years
  - *Plans to lower minimum age to 12 years where pediatric dose defined*

Urgency of the Project: 5 Years Down the Road

- Have we begun to change protocols
- Are protocols enrolling more patient
- Industry conducting studies with bro
- Are young investigators writing proto
- FDA approval of drugs in these popu
- I believe we will look back at this en
- It won't take 108 years

Friends Annual Meeting

Paul J. Hesketh, MD
Lahey Health Cancer Institute

Addressing Eligibility Criteria as a Barrier to Patient Accrual in the NCI's National Clinical Trials Network (NCTN)

Paul J. Hesketh, MD

Chair, Lahey Health Cancer Institute

Burlington, MA

NCI National Clinical Trials Network

a National Cancer Institute program

Overview

- NCTN Accrual Core Team (Network ACT)
  - Eligibility task force
- SWOG
  - Evolution of key eligibility criteria in phase III NSCLC trials
  - Eligibility/mandatory testing modifications in phase III trials with demonstrable improvement in accrual
- ECOG-ACRIN
  - Addressing the issue of prior malignancy history
- Alliance for Clinical Trials in Oncology (Alliance)
  - Eligibility vs. “on-study guidelines”
- NRG Oncology
  - New guidelines

SWOG Phase III NSCLC Trials: Evolution of Selected Eligibility Criteria

- **S9509**
  - Phase III Trial of Paclitaxel plus Carboplatin versus Vinorelbine and Cisplatin in Untreated Advanced NSCLC
- **S1400**
  - Biomarker-Driven Master Protocol for Previously Treated Squamous Cell Lung Cancer (LUNG-MAP)
- **S1403**
  - Randomized Phase II/III Trial of Afatinib Plus Cetuximab Versus Afatinib Alone In Treatment-Naïve Patients With Advanced, EGFR Mutation Positive NSCLC

Evolving Eligibility Criteria in SWOG Phase III NSCLC Trials (1995 -2014)

CRITERIA	S9509	S1400	S1403
Brain metastases	No	Yes (treated)	Yes (asymptomatic)
Prior Malignancies	Skin (b/s), cervical (is) others NED > 5 years	Skin (b/s), cervical (is) Stage I/II in CR others NED > 5 years	Skin (b/s), cervical (is) Stage I/II in CR others NED > 3 years
Liver function tests	Single criteria	Two criteria (with or without mets	Two criteria (with or without mets
HIV positive	No mention	Yes (controlled)	No
Time limit imaging studies (meas dis)	28 days	28 days	42 days
Prior radiotherapy	≥ 3 weeks	> 2 weeks	> 7 days

Enhanced Accrual After Modification of Eligibility Criteria and Mandatory Tests (SWOG Trials)

Trial	Disease Site	Modification	Impact
S1314	Bladder	Tissue blocks → slides; remove minimum number of cystectomies/per year by urologist	01/14 – 03/15 1 pts/mo 07/15 – 06/16 7 pts/mo
S0226	Breast	PK testing made optional	06/04 – 10/05 6 pts/mo 11/05 – 06/09 14 pts/mo
S0702	ONJ	Remove requirement for baseline dental exam	11/10 – 10/11 52 pts/mo 02/12 – 01/13 89 pts/mo
S0805	ALL (transpl)	Increased age limit from 50 – 60; allowed entry of patients already receiving chemotherapy	Accrual enhanced post amendments
S0438	Melanoma	Removed requirement for PET scans at baseline, week 3 and week 9	08/07 – 03/08 0 pts 08/08 – 01/09 14 pts/mo

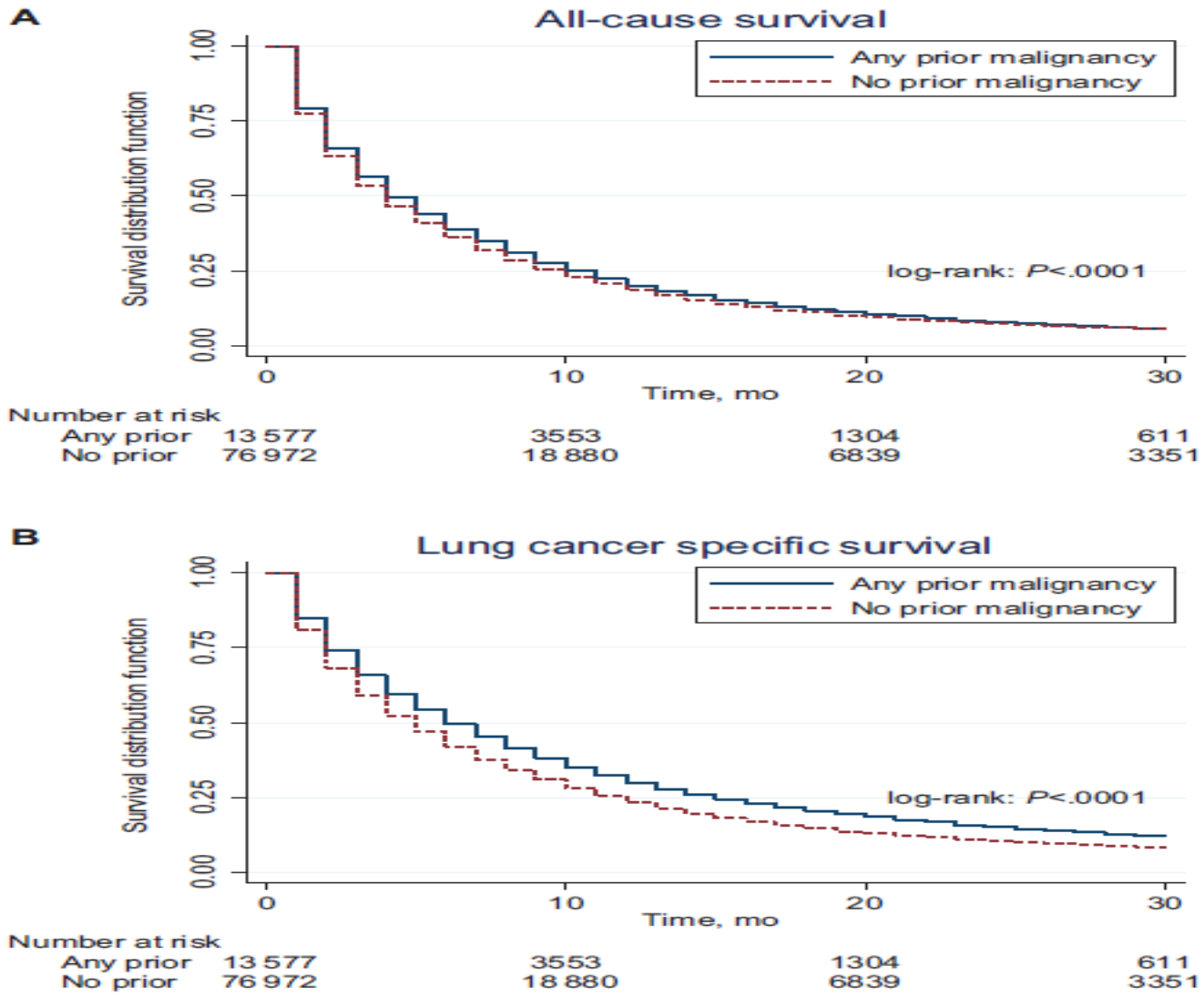
Addressing Prior History of Malignancy as a Barrier to Patient Accrual: ECOG-ACRIN Efforts

David Gerber MD and colleagues at UT Southwestern Medical Center

ECOG Lung Cancer Trial Analysis

- Reviewed cancer-related eligibility criteria in 51 ECOG lung cancer (all histologies, phases, stages) trials with a target enrollment of > 13,000
- Used Medicare – SEER data to estimate exclusion rate because of a prior cancer
- Over 80% of lung trials exclude prior cancers
- Almost 85% of prior cancers are in situ, localized or regional stage
- Prostate, other GU and GI most common primary sites
- Up to 18% of patients are excluded from lung cancer trials due to a history of a prior cancer

Prior Malignancy Impact on Survival in Stage 4 Lung Cancer



Gerber DE JNCI 2015 107(4)

ECOG Lung Cancer Trial Analysis: Implications

- ECOG/ACRIN Stage 4 NSCLC protocols
  - Original exclusion – " No prior cancers within 5 years"
  - Current exclusion – " No clinically active cancer"
- ALCHEMIST trial (stage 1-3 resected NSCLC)
  - Current exclusion – "No prior or concurrent cancer with 5 years, except non-melanoma skin carcinoma or in-situ carcinomas"
  - Proposed exclusion – " No locally advanced or advanced cancer requiring systemic therapy within 5 years"

Alliance: Improving Eligibility in Clinical Trials

- All eligibility criteria evaluated using three principles
  - Criteria should be absolutely required for anticipated scientific inference or patient safety.
  - Criteria should be unambiguously defined and capable of verification at time of audit
  - Criteria should not be regulatory, legal, or other requirement
- CALGB/Alliance studies incorporate “on-study guidelines”
  - Guidelines are not exclusion criteria, but allow physician judgment to prevail

George SL Reducing patient eligibility criteria in cancer clinical trials. J Clin Oncol. 1996 Apr;14(4):1364-70.

Alliance: Improving Eligibility in Clinical Trials

C9710

PHASE III RANDOMIZED STUDY OF CONCURRENT TRETINOIN AND CHEMOTHERAPY WITH OR WITHOUT ARSENIC TRIOXIDE (As_2O_3) (NSC # 706363) AS INITIAL CONSOLIDATION THERAPY FOLLOWED BY MAINTENANCE THERAPY WITH INTERMITTENT TRETINOIN VERSUS INTERMITTENT TRETINOIN PLUS MERCAPTOPURINE AND METHOTREXATE FOR PATIENTS WITH UNTREATED ACUTE PROMYELOCYTIC LEUKEMIA

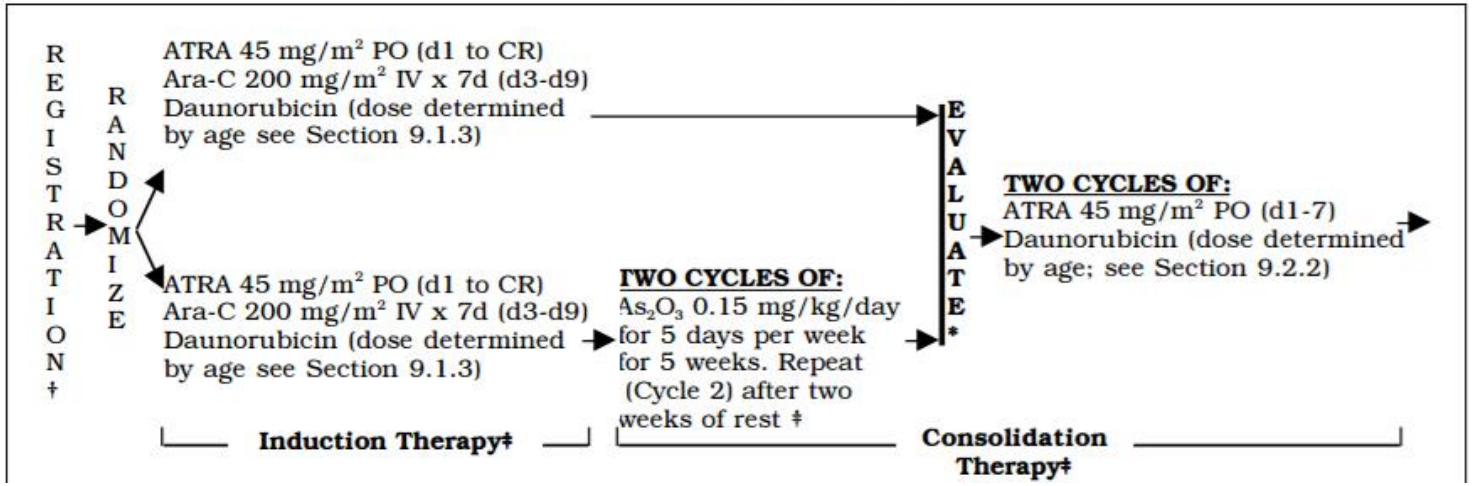
Eligibility Criteria (see Section 5.0):

The only explicit eligibility criteria on this study are defined below.

- Diagnosis of acute promyelocytic leukemia (APL) with proof of APL morphology (FAB-M3) confirmed by RT-PCR assay (see Section 5.1).
- Prior Treatment: No systemic definitive treatment for APL, including cytotoxic chemotherapy or retinoids. Prior therapy with corticosteroids, hydroxyurea or leukapheresis will not exclude the patient.
- Non-pregnant, non-nursing. Treatment under this protocol would expose an unborn child to significant risks. Patients should not be pregnant or plan to become pregnant while on treatment (see Section 5.3).

See also Section 4.0 for general guidelines on the type of patient appropriate for this study and Section 6.0 for other requirements.

TREATMENT SCHEMA



NRG Efforts to Improve Eligibility

- Developing guidelines to broaden, or if appropriate eliminate, specific date ranges for completion of required laboratory and imaging tests.
- Developing guidelines to correlate testing to standards of care for specific disease sites and across disease sites as appropriate.

Conclusions

- Restrictive eligibility criteria constitute a barrier to successful completion of clinical trials
- All NCTN members are involved in efforts to appropriately broaden eligibility criteria and carefully review mandatory tests
- Efforts to address restrictive criteria have resulted in enhanced accrual on multiple NCTN trials
  - Brain metastases
  - Prior history of cancer
  - Excessive imaging requirements
  - Bio-sample submission requirements
  - Liver function criteria
  - Expanding age range
- Important area for additional efforts to balance the critical dynamic between maintaining patient safety and ability to define therapeutic efficacy and the imperative to complete accrual in a timely manner

Friends Annual Meeting

Pratik Multani, MD
Ignyta, Inc.

Blazing a New Future
for Patients with Cancer™

ignyta®

Presentation at FOCR Symposium: Panel 1

November 2016

Entrectinib: an Investigational, Potentially First- and Best-in-Class TRK Inhibitor and Best-in-Class ROS1 Inhibitor

Target	TRKA	TRKB	TRKC	ROS1	ALK
IC_{50}* (nM)	1.7	0.1	0.1	0.2	1.6

- Most potent, orally available pan-TRK-inhibitor in clinical development; active against most known TRK-resistant mutants
- 30x more potent against ROS1 than crizotinib; high potency against ALK
- Designed to cross blood brain barrier (BBB) and to address primary brain tumors and secondary CNS metastases
- Entrectinib-mediated inhibition of oncogenic fusion proteins results in rapid tumor response in preclinical models and in selected patient populations

* Biochemical kinase assay

Gene Rearrangements Targeted by Entrectinib Are Present in a Large Number of Tumors

	NTRK1	*NTRK2*	*NTRK3*	*ROS1*	*ALK*
NSCLC (adeno, large cell NE)	1-3%	<1%	<1%	1-2%	3-7%
CRC	1-2%		1%	1-2%	1-2%
Salivary gland – mammary analog secretory carcinoma [MASC]			90-100%		
Salivary gland – NOS			3%		
Sarcomas (including GIST)	1-9%		2-11%	2-3%	1-5%
Astrocytoma		3%			
Glioblastoma	1-3%			1%	
Melanoma (Spitz)	16%			17%	10%
Cholangiocarcinoma	4%			9%	2%
Papillary thyroid carcinoma	5-13%		2-14%		7%
Breast – secretory carcinoma			92%		
Breast – NOS					2%

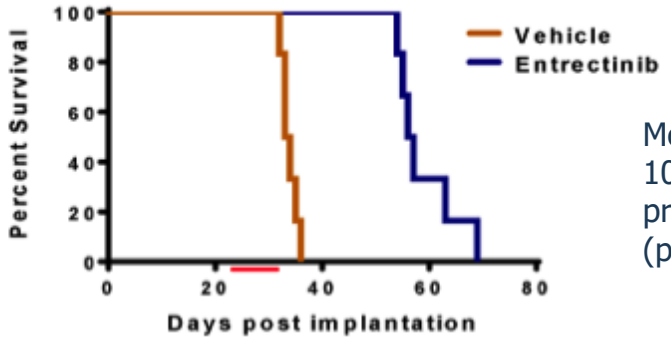
NOS: not otherwise specified

Entrectinib Was Specifically Designed to Cross the Blood-Brain Barrier to Address CNS Disease

Entrectinib demonstrates significant BBB penetration in 3 mammalian species

Brain/blood ratio:
- Mouse: 0.4
- Rat: 0.6 – 1.0
- Dog: 1.4 – 2.2

CNS penetration of entrectinib achieves tumor shrinkage and leads to a robust survival benefit in preclinical model of CNS tumors



Mouse model of intracranial lung cancer tumors: 10 days of oral entrectinib treatment led to prolonged survival of 57 days vs. 34 days ($p<5x10^{-4}$)

Phase 1 Studies
Updated data as of March 7, 2016

ALKA-372-001

- Dosing: intermittent and continuous
- *NTRK1/ROS1/ALK* alterations
- Italy
- 54 patients

STARTRK-1

- Dosing: continuous
- *NTRK1/2/3*, *ROS1* or *ALK* alterations
- US, EU, Asia
- 65 patients

Total clinical experience: 119 patients
45 patients treated with RP2D*: 600 mg PO once daily

"Phase 2-eligible population": 25 patients

- *NTRK1/2/3*-, *ROS1*-, or *ALK*-rearranged solid tumor
- Naïve to prior TRK/ROS1/ALK inhibitors, as applicable
- Treated at or above RP2D*

Response Evaluation

- RECIST v1.1, locally assessed and confirmed: **24 patients**
- Volumetric assessment: **1 patient with primary brain tumor****

Note: * RP2D = Recommended Phase 2 Dose
** RECIST criteria not validated in primary brain tumors (FDA-AACR Brain Tumor Endpoints Workshop 2006)

Treatment-Related Adverse Events at RP2D
>10% incidence; grades according to NCI CTCAE v4.0

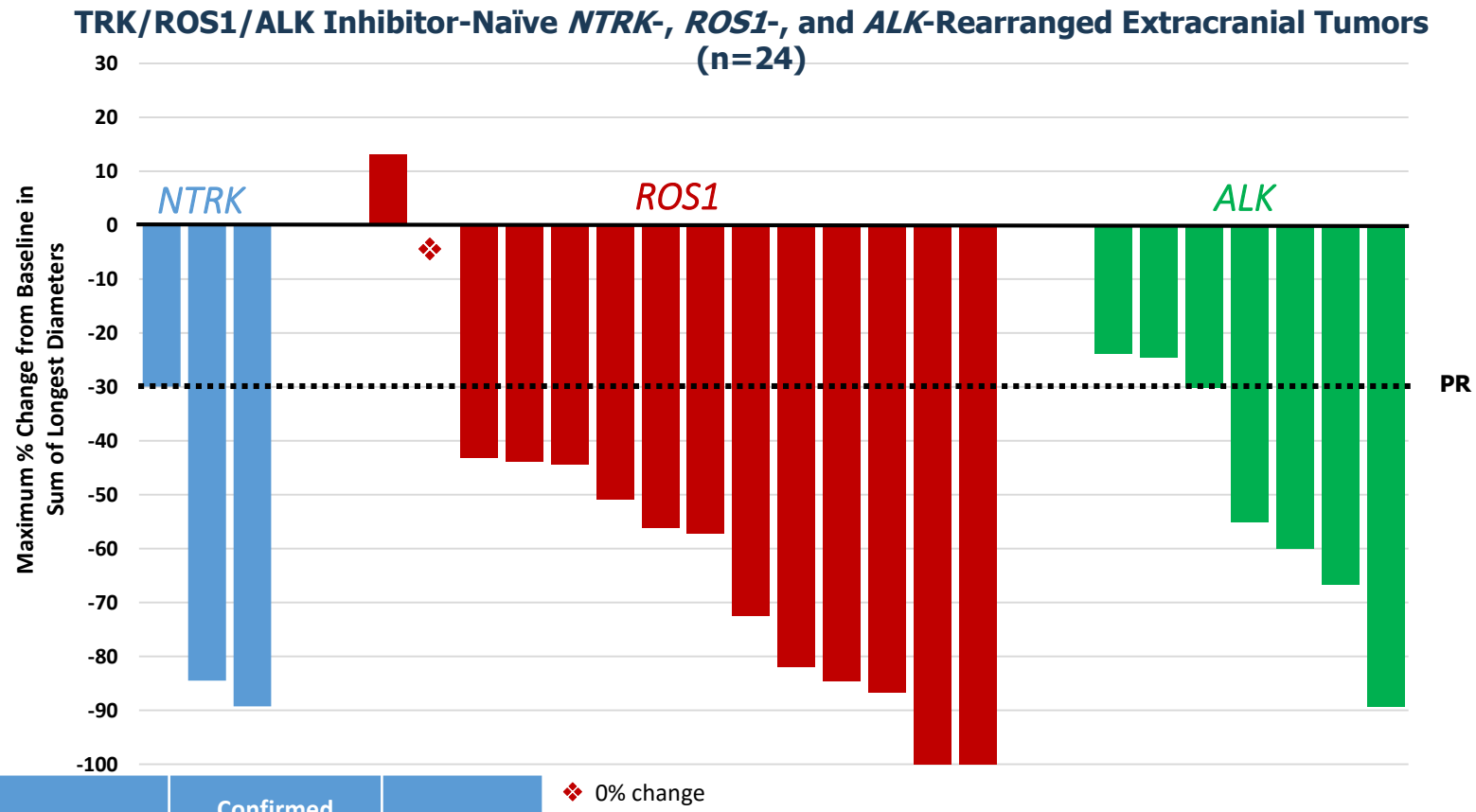
- No cumulative toxicity
- No renal toxicity
- No QTc prolongation
- No hepatic toxicity
- No AEs ≥ Grade 4
- All AEs reversible with dose modification

Adverse Events (AEs) at the RP2D (n=45)

Adverse Event Term, n (%)	Grades 1-2	Grade 3	Total
Dysgeusia	21 (47)		21 (47)
Fatigue/Asthenia	17 (38)	1 (2)	18 (40)
Constipation	10 (22)		10 (22)
Weight Increased	8 (18)	1 (2)	9 (20)
Diarrhea	7 (16)	1 (2)	9 (18)
Nausea	8 (18)		8 (18)
Myalgia	7 (16)		7 (16)
Paresthesia	7 (16)		7 (16)
Dizziness	6 (13)		6 (13)
Peripheral Sensory Neuropathy	4 (9)	2 (4)	6 (13)
Anemia	2 (4)	3 (7)	5 (11)
Dysphagia	4 (9)	1 (2)	5 (11)
Vomiting	5 (11)		5 (11)

(≥10% incidence, grades per NCI CTCAE v4.0, data as of March 7, 2016)

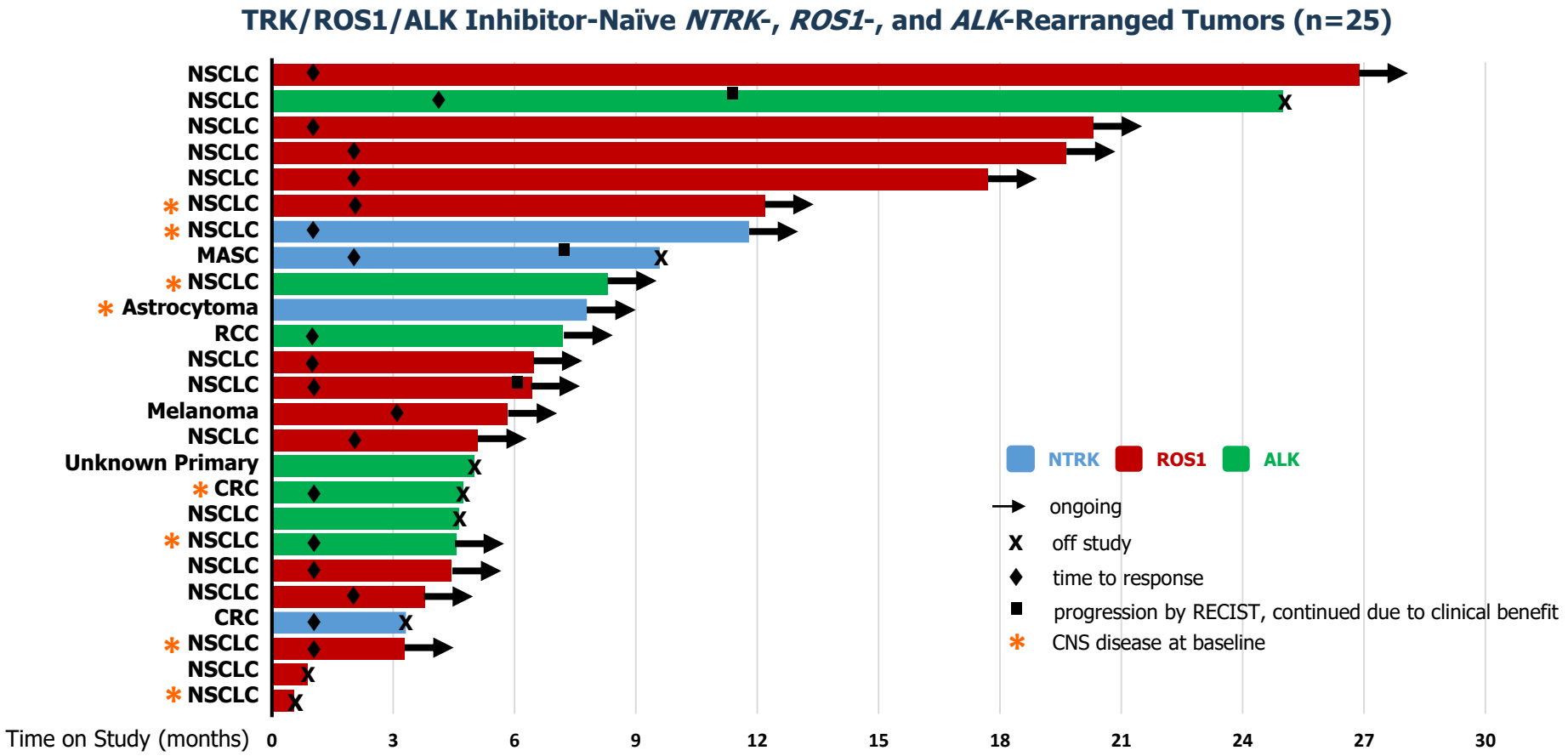
Antitumor Activity in TRK/ROS1/ALK Inhibitor-Naïve Patients with *NTRK1/2/3*, *ROS1*, or *ALK* Gene Rearrangements



Fusion	Confirmed Responses (n)	ORR (%)
NTRK1/3	3/3	100%
ROS1	12/14	86%
ALK	4/7	57%

Note: Data cutoff 07 March 2016

Antitumor Activity in TRK/ROS1/ALK Inhibitor-Naïve Patients with *NTRK1/2/3, ROS1,* or *ALK* Gene Rearrangements



The median duration of response has not been reached (95% CI: 6 months, NR)

Note: Data cutoff 07 March 2016

Ignyta Case Report: Mr. Z

Nov 2013 → **March 2015**

- 46M patient with metastatic NSCLC, first diagnosed in November 2013
- 30 pack-year smoking history

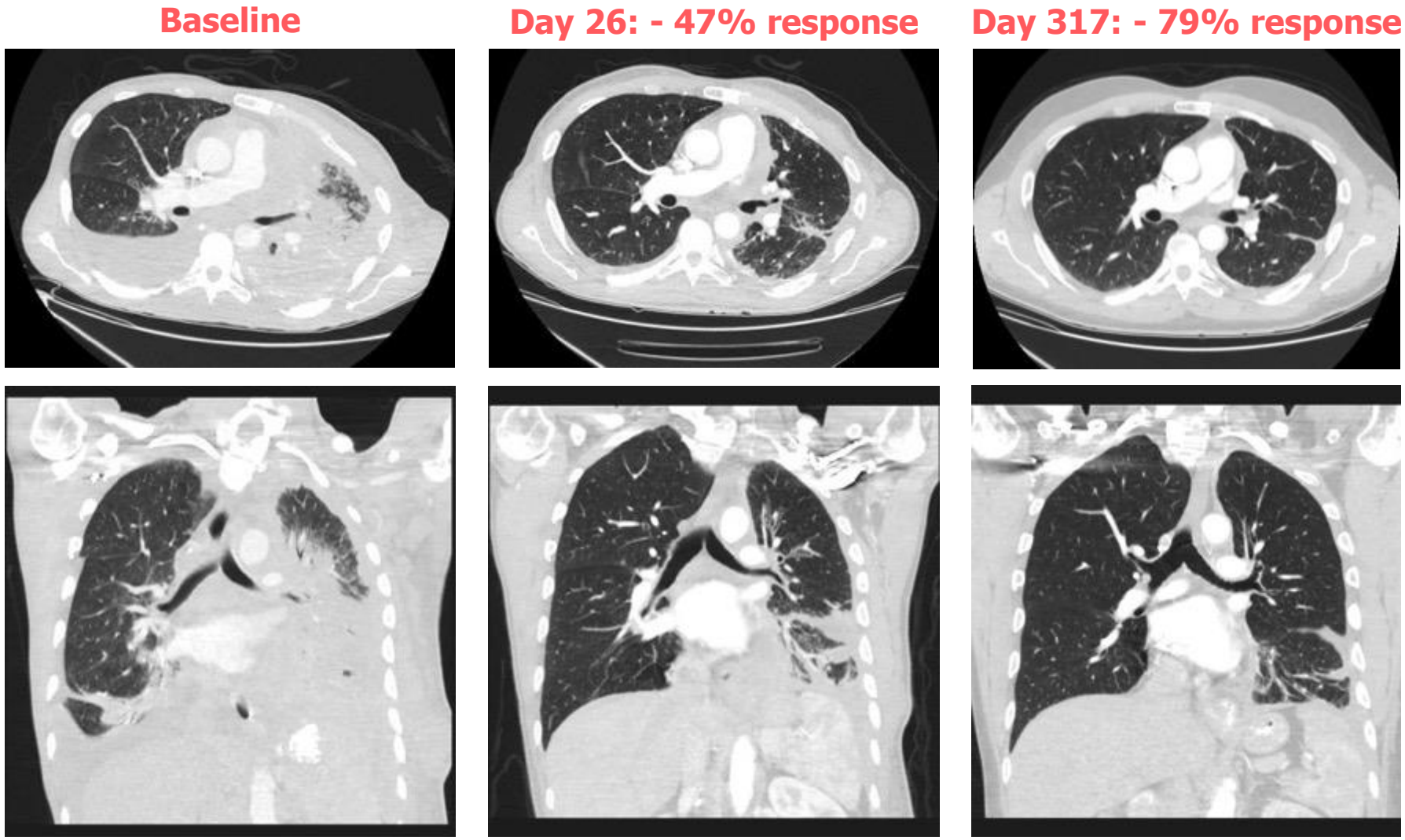
Prior therapies

- carboplatin/pemetrexed
- pembrolizumab
- docetaxel
- vinorelbine

- ECOG performance status: 2
- Required supplemental O_2
- Significant pain and dyspnea due to widely metastatic disease
- Staging head CT revealed numerous (15 to 20) asymptomatic brain metastases
- In hospice

Identified to have tumor harboring *SQSTM1-NTRK1* fusion;
Enrolled in Ignyta's STARTRK-1 study at MGH in March 2015

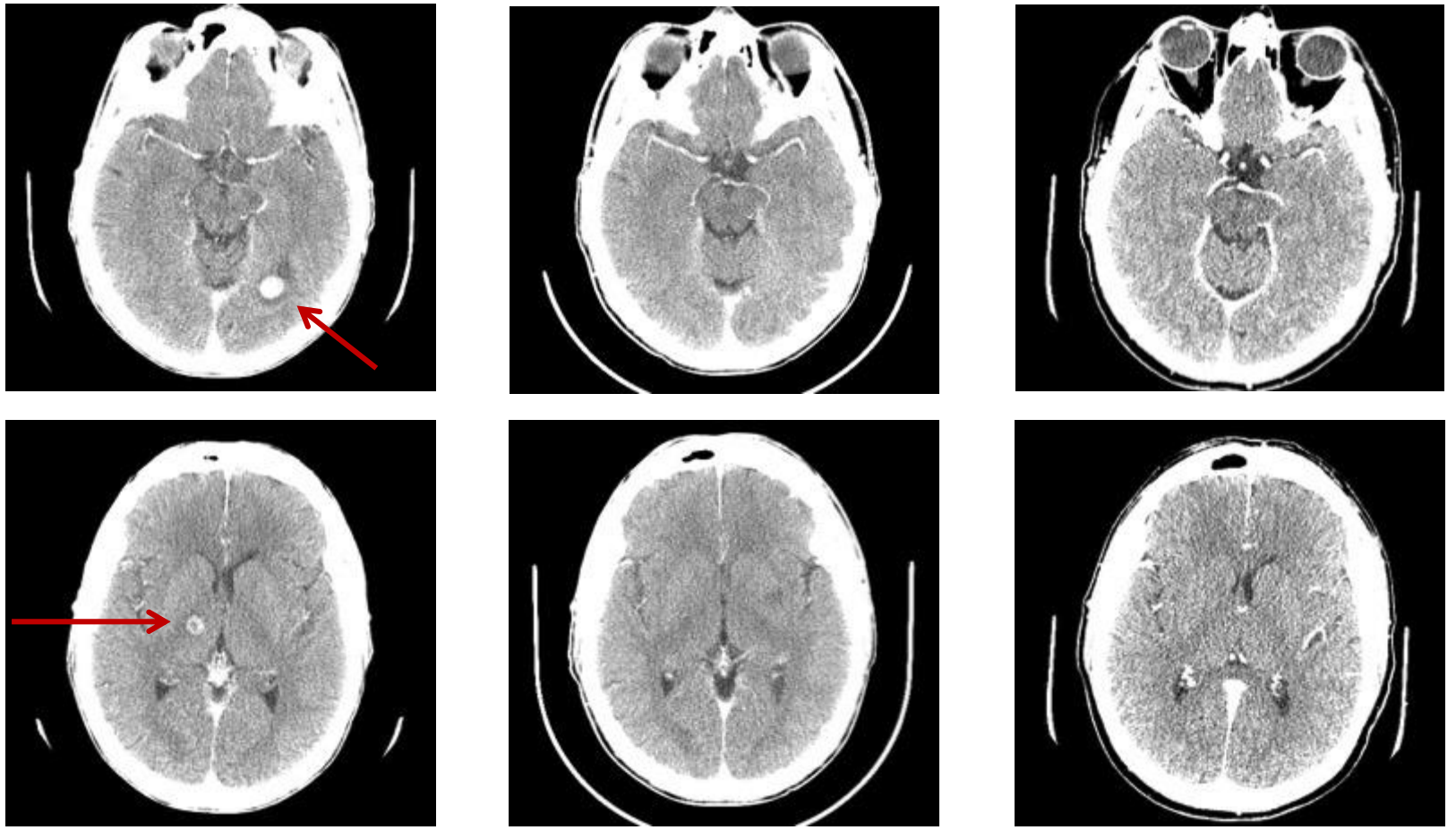
Clinical Response to Entrectinib in 46M Patient with *NTRK1*-Rearranged NSCLC



Source: Images courtesy of A. Shaw, MD, PhD and A. Farago, MD, PhD (MGH);
Note: Individual results may not be representative of results in other patients.

Complete Response of All Brain Metastases in 46M Patient with *NTRK1*-Rearranged NSCLC

Baseline (15-20 mets) | **Day 26 (CR)** | **Day 155 (CR)**



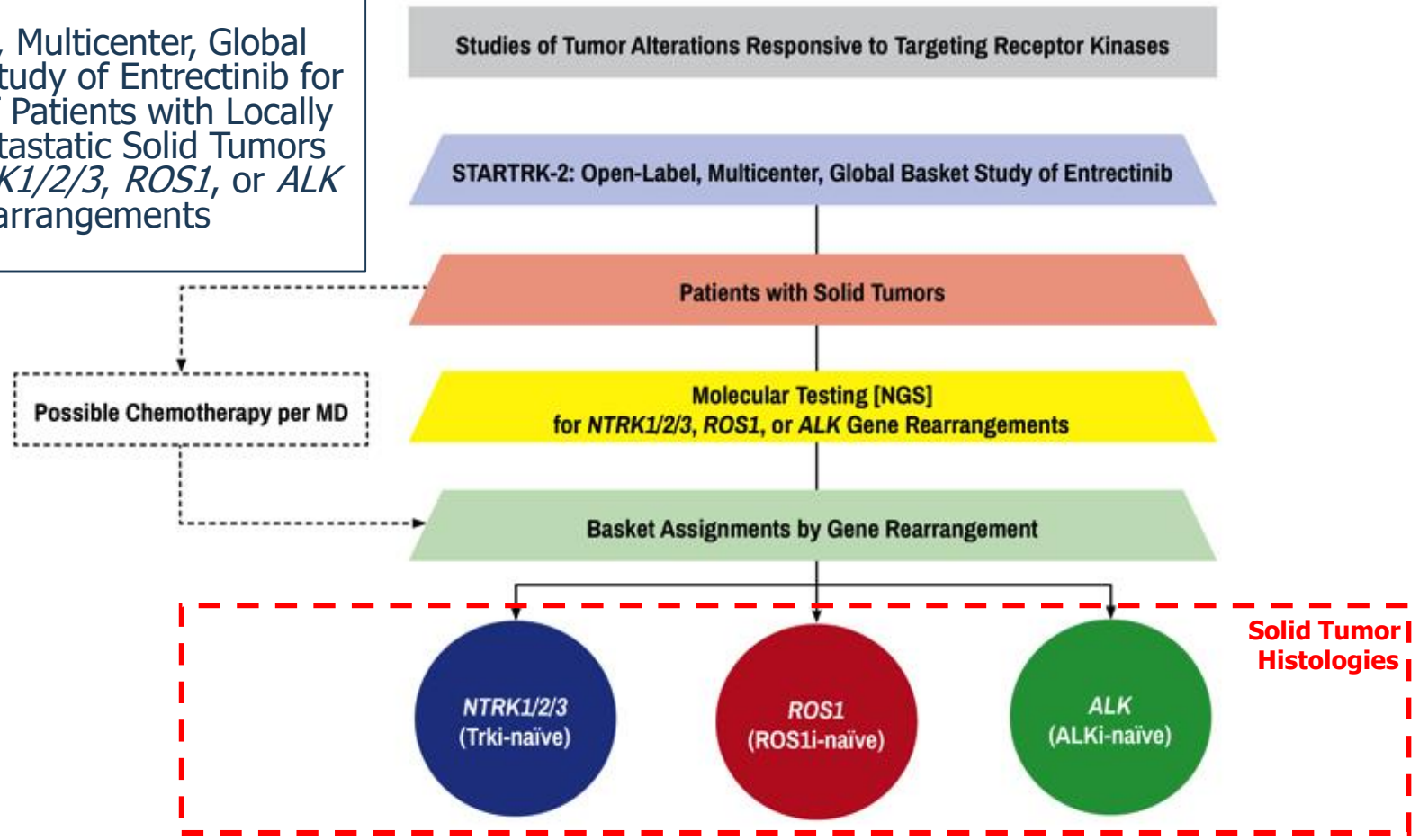
CNS complete response persists at Day 317

Source: Images: Farago and Shaw, MGH
Note: Individual results may not be representative of results in other patients.

STARTRK-2: Entrectinib Global, Phase 2 Pivotal Basket Study

STARTRK-2

An Open-Label, Multicenter, Global Phase 2 Basket Study of Entrectinib for the Treatment of Patients with Locally Advanced or Metastatic Solid Tumors that Harbor *NTRK1/2/3*, *ROS1*, or *ALK* Gene Rearrangements



Global Study: open at 100+ sites in 12 countries

STARTRK-2: Principles of Study Eligibility

Draft Issue Brief on Eligibility

- *Allow broad enrollment while restricting primary analysis to defined patient population*
  - *Protect integrity of trial while enabling data collection in broader populations*
  - *Data may be helpful to inform safe clinical use in "real-world" patients*

STARTRK-2 Approach

- Broad I/E criteria
  - Consider tumor type, age, minimal organ function, prior treatment history, CNS involvement, etc.
- Restrict to only what is absolutely necessary
  - To interpret efficacy
  - To interpret safety
- Acknowledge that certain patients may contribute only to a subset of endpoints
  - E.g., non-measurable but evaluable disease: PFS, OS, safety, PK
- Consider compassionate use requests
  - Accommodate without compromising primary study objectives

STARTRK-2: Main Eligibility Criteria

Criteria

- Histologically- or cytologically-confirmed diagnosis of locally advanced or metastatic **solid tumor** that harbors an NTRK1/2/3, ROS1, or ALK gene rearrangement (excluding ALK NSCLC)
- No prior approved or investigational TRK, ROS1, or ALK inhibitors in patients who have tumors that harbor those respective gene rearrangements
  [no other restriction on prior treatment history]
- Eastern Cooperative Oncology Group (ECOG) **performance status ≤ 2** and minimum life expectancy of at least 4 weeks

Basis

- Rarity of the target fusions
- Absence of effective, approved therapies (except ROS1 NSCLC)
- Substantial Phase 1 safety experience in patients with > 4 prior therapies, multiple histologies, multiple sites in US and EU

STARTRK-2: CNS Involvement

Criteria

- **Patients with CNS involvement**, including leptomeningeal carcinomatosis, which is either asymptomatic or previously-treated and controlled, are allowed
  - The use of seizure prophylaxis is allowed as long as patients are taking non-enzyme-inducing anti-epileptic drugs (non-EIAEDs)
  - Patients requiring steroids must be at stable or decreasing doses for at least 2 weeks prior to the start of entrectinib treatment
    [No specified max steroid dose]

Basis

- Evidence of BBB-penetration of entrectinib in multiple nonclinical species
- Multiple examples of clinical responses in the CNS in patients with primary or secondary CNS malignancy
- Multiple patients enrolled in Phase 1 with CNS involvement and concomitant use of non-EIAEDs and steroids

STARTRK-2: Minimal Organ Function and Concomitant Infections

Criteria

- No requirements for minimal **renal function**
- No requirements for minimal **hematologic function**
- Exclusion: known active **infections** that would interfere with the assessment of safety or efficacy of entrectinib (bacterial, fungal, or viral, including human immunodeficiency virus positive)

Basis

- Human AME study showed ~3% of entrectinib and its metabolites are excreted in the urine
- Phase 1 experience showed minimal hematologic toxicity
  - Most frequent hematologic AE was anemia, Grade 3 in 3%
- No evidence of hepatic toxicity in toxicology studies and human clinical trials

STARTRK-2: Age Range

- Explored potential to lower age limit of STARTRK-2 to age 12
- Challenges
  - Timing: Adult RP2D identified before pediatric RP2D
  - Global footprint of STARTRK-2: No guarantee that such a change would be acceptable in all jurisdictions
  - Investigators: Pediatric vs. Adult
  - Institutions: Different set of cancer centers, often with separate IRB/review processes
  - Operational: Any amendments to the protocol to incorporate changes to pediatric or adult management would impact the whole study

- Solution
  - Separate Phase 1/1b pediatric protocol: *STARTRK-Next Generation*
  - Leverage institutions involved in STARTRK-2 as much as possible but allow flexibility to go to major pediatric cancer centers
  - Raise upper age of pediatric trial to age 22

“Non-Evaluable for the Primary Endpoint” Basket

- Exploratory
- Patients who have an NTRK1/2/3, ROS1, or ALK gene rearrangement but do not meet all inclusion or exclusion criteria
- These patients are not assessable for the primary endpoint but will mainly contribute to assessment of safety, PK, and other secondary endpoints
- Examples of such patients include, but are not limited to:
  - ECOG performance status > 2
  - Dual primary cancers where one cancer’s mutation status is unknown
  - Patients with extracranial solid tumors without RECIST v1.1-defined measurable disease
- Way to incorporate compassionate use requests and “real-world” patient experience, while maintaining integrity of the main data set, and permitting data collection of these patients (as much as feasible)
- Option for single-patient protocols (SPPs) for exceptional circumstances (e.g., hematologic malignancies)

Friends Annual Meeting

Rajeshwari Sridhara, PhD
US Food & Drug Administration

Expansion of Eligibility Criteria: Trial Design Considerations

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Director, Division of Biometrics V

November 16, 2016

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

Protocols Submitted in 2015*

- Total # of INDs submitted ≈ 1031; 68% Research INDs, 32% Commercial INDs

Of the commercial INDs:

- 3.7% included pediatric patients
- 60% required ECOG/WHO PS of 0-1; 35% required PS 0-2
- 77% excluded known, active, or symptomatic CNS or brain metastases; 47% allowed treated or stable brain metastases
- 84.2% excluded known or active HIV patients; 1.7% allowed stable disease and patents with adequate CD4 counts

* Research project conducted by Susan Jin, DBV, CDER, FDA

Expansion of Eligibility Criteria

- Without compromising safety
- Expand to include patients with, for example, PS 3, brain metastases, HIV, men with breast cancer, or pediatric patients where applicable, elderly patients, etc.
- What are the design options for such a trial and how to interpret the data from such a clinical trial

Trial Design Options

1. Randomized Clinical Trial
   - Population: defined by restricted eligibility criteria (ElgPop) + expanded population (ExpPop)
   - Stratification factors: ElgPop and ExpPop
   - ITT population = ElgPop + ExpPop; Modified ITT (MITT) population = ElgPop
   - Primary analysis based on MITT (the primary indicated population)
   - Hierarchical testing: ITT after MITT; if sample size is adequate and hypothesis driven then ExpPop tested separately

Trial Design Options

2. Simultaneous RCT in ElgPop and single arm cohort in the ExpPop
   - ITT population = ElgPop in the RCT; analyzed separately
   - Single arm ExpPop – descriptive statistics

Things to Consider

1. Who should be in the ExpPop cohort?
2. Trial Option 1
   - Proportion of patients in ElgPop > ExpPop (example, 80:20)
   - Primary hypothesis, Type I and Type II errors, number of events for the final analysis, all based on ElgPop
   - Hierarchical testing feasible? – what if more events in the ExpPop cohort
   - Limit number of patients in ExpPop cohort
3. Trial Option 2
   - ExpPop enrolled only in certain sites
   - Difficult to interpret toxic events, in particular deaths without a control arm in the ExpPop patients

Labeling Claim in Expanded Population

- Case specific: depends on available treatment, prevalence of the disease, magnitude of treatment effect and toxicity
- Indication in the Eligible (MITT) Population will be purely based on the primary analysis in the MITT population
- Report efficacy in the ITT population and ExpPop cohort; Inference in the ExpPop may not always be possible. If there is substantial evidence then expansion of indication to the ITT population can be considered
- Reporting separately toxicity observed in the ExpPop population can be considered


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Panel Discussion

- **Edward Kim, MD**; Levine Cancer Institute, Carolinas Healthcare System
- **Paul Hesketh, MD**; Lahey Health Cancer Institute
- **Pratik Multani, MD**; Ignyta
- **Rajeshwari Sridhara**, PhD; FDA
- **Nancy Roach**; Fight Colorectal Cancer
- **Gwynn Ison, MD**; FDA
- **Eric Rubin, MD**; Merck
- **Andrea Denicoff, RN**; NCI
- **Elizabeth Garrett-Mayer, PhD**; Medical University of South Carolina

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