

NCI-Supported Clinical Research During the COVID-19 Pandemic

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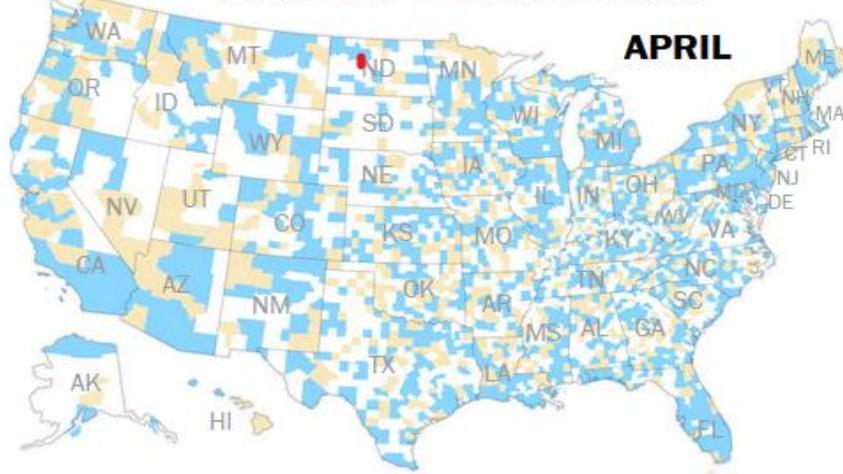
Joint NCAB/BSA Meeting

June 15, 2020

Effect of COVID-19 on US Health Care System

Hospital traffic compared to 2019

Down 33-50% Down 50% or more



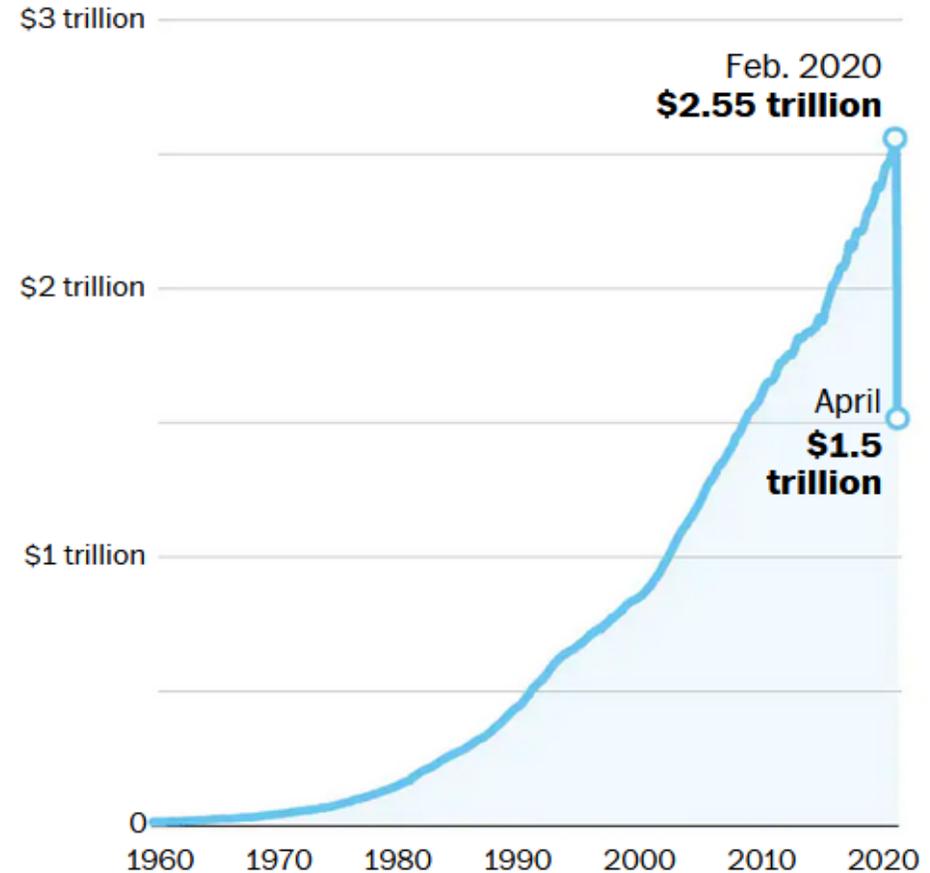
Where hospitals lose money

Share with negative net income



Personal health-care spending

Jan. 1960-April 2020

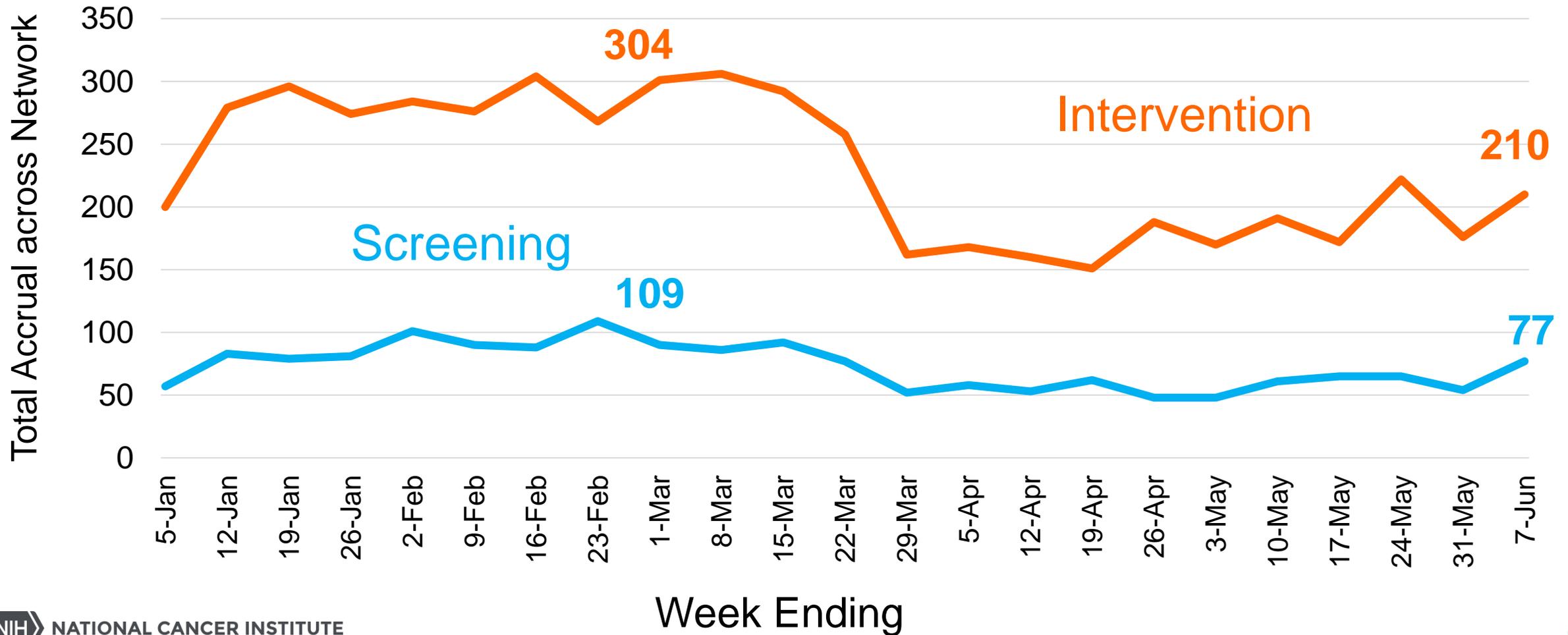


Note: Spending amounts are BEA annual estimates.

Operational Impediments to Clinical Cancer Research

- Decreased efficiency of physical distancing, limited patient contact, and necessary use of PPE
- Operational limitations to both outpatient clinic and inpatient resources
- Reprogramming of research staff to COVID-19-related duties
- Reduced clinical laboratory throughput
- Decreased availability of imaging and IR services
- Practical impediments to specimen handling
- Travel restrictions
- Decreased investigational pharmacy staffing
- Suspension of translational research laboratory activities
- Decreased IRB throughput

NCI National Clinical Trials Network (NCTN) Accrual to “Screening” and “Intervention” Steps in Trials by week



NCI's Clinical Trials: Response to COVID-19

- National COVID-19 natural history study
- BTKi for Severe COVID-19
- Tocilizumab compassionate use study

Overview of NCI COVID-19 in Cancer Patients Study (NCCAPS):

*A Longitudinal
Natural History Study*

Brian Rini and Lorissa Korde, PIs

Background: COVID-19 in Cancer Patients

Study Rationale:

- COVID-19 may **disrupt** cancer-directed therapy, possibly resulting in worse outcomes.
- **Long-term outcomes** of patients with COVID-19 and cancer are unknown.
- Results from this natural history study will **guide future care** for cancer patients who acquire COVID-19.

- Cancer patient risk factors:
 - Age
 - Comorbidities
 - Exposure
 - ↓ Immunity
- China: cancer patients had higher risk of severe events:
 - admission to the ICU
 - need for mechanical ventilation
 - Death
- CCC-19: 30-day mortality of 13%
 - Higher for older age, smokers, active treatment

NCCAPS Natural History Study Goals

- Enroll a large cohort of patients undergoing cancer therapy who test positive for SARS-CoV-2 to characterize factors associated with COVID-19 severity.
- Describe modifications to cancer treatment made due to COVID-19.
- Evaluate the association of COVID-19 with cancer outcomes in clinico-pathologic subgroups.
- Assess anti-SARS-CoV-2 antibody development, cytokine abnormalities, and genetic polymorphisms associated with severe COVID-19.
- Create a bank of clinical data, research blood specimens, and radiological images for future research.

NCCAPS Participating Sites

**ETCTN
sites**

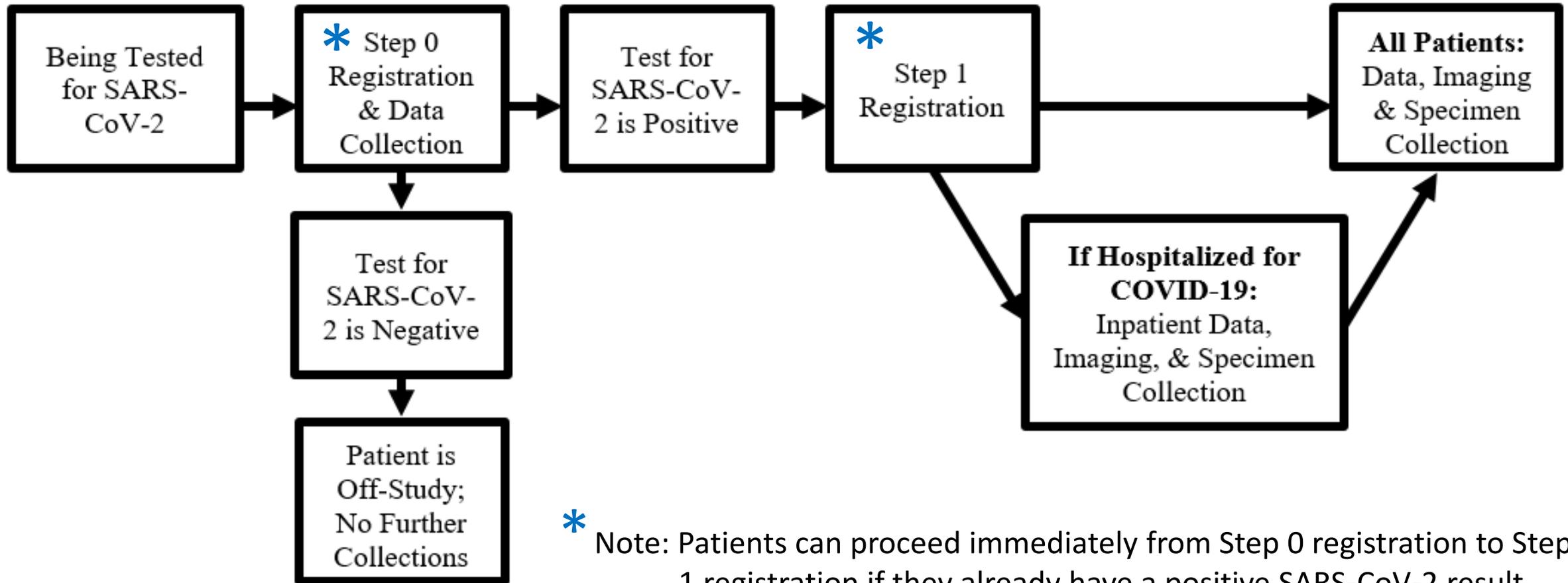
**NCORP
sites**

**NCTN
sites**

- NCI's Experimental Therapeutics Clinical Trials Network (ETCTN)
- The NCI Community Oncology Research Program (NCORP)
- NCI's National Clinical Trials Network (NCTN)

NCCAPS Schema

- Step 1 Planned Accrual: 2,000 patients
- Follow outcomes for up to 2 years



- * Note: Patients can proceed immediately from Step 0 registration to Step 1 registration if they already have a positive SARS-CoV-2 result.

**Positive test result may be no earlier than 14 days prior to Step 1 registration.
Patients with positive SARS-CoV-2 results greater than 14 days old are not eligible.**

NCCAPS: Measures to Address Site Feasibility Issues

- Informed consent may be done remotely.
- Patients are not required to have any extra visits for this study.
 - Research blood specimens will be collected at the same time blood is drawn as part of regular clinical care.
 - Imaging scans collected for banking are those scans being done as part of clinical care.
- Research bloods do not require on-site processing.
Specimen kits will be provided, including shipping to the biorepository.
- Sites receive full accrual credit for enrollments to Step 1, partial credit for step 0. (per the ETCTN, NCORP, and NCTN guidelines).

Upcoming protocol goals for NCCAPS

Amendment 1:

- Open enrollment to pediatric patients
- Addition of QoL assessments (outpatient)
- Guidelines for imaging analysis

Future amendments:

- Additional blood collections for sites with on-site processing capability
 - Red-top serum tubes for neutralizing antibody studies
 - Coagulation assays

NCCAPS Investigators/Rapid Progress

- **Protocol Chairs:**

- Larissa A. Korde, MD, MPH (NCI)
- Brian I. Rini, MD, FACP, FASCO (Vanderbilt)

- **Study Statistician:**

- Larry Rubinstein, PhD (NCI)

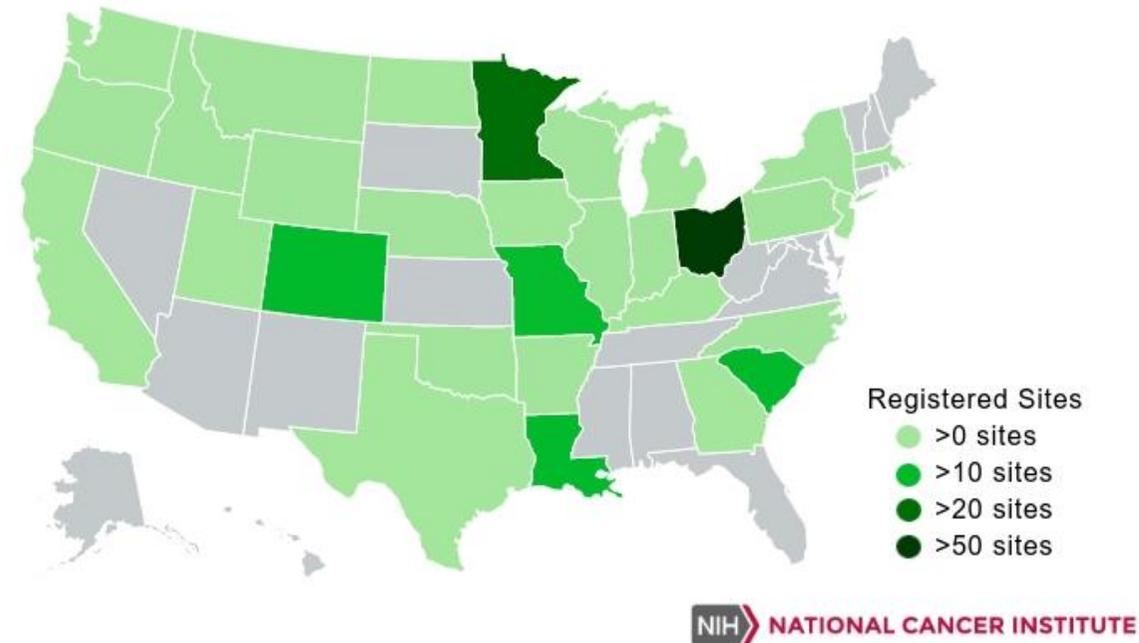
- **Translational Co-Chair:**

- Lyndsay Harris, MD (NCI)

- **Imaging Co-Chairs:**

- Michael V. Knopp MD, PhD (Ohio State)
- Lalitha K. Shankar, MD, PhD (NCI)

NCCAPS Study Sites

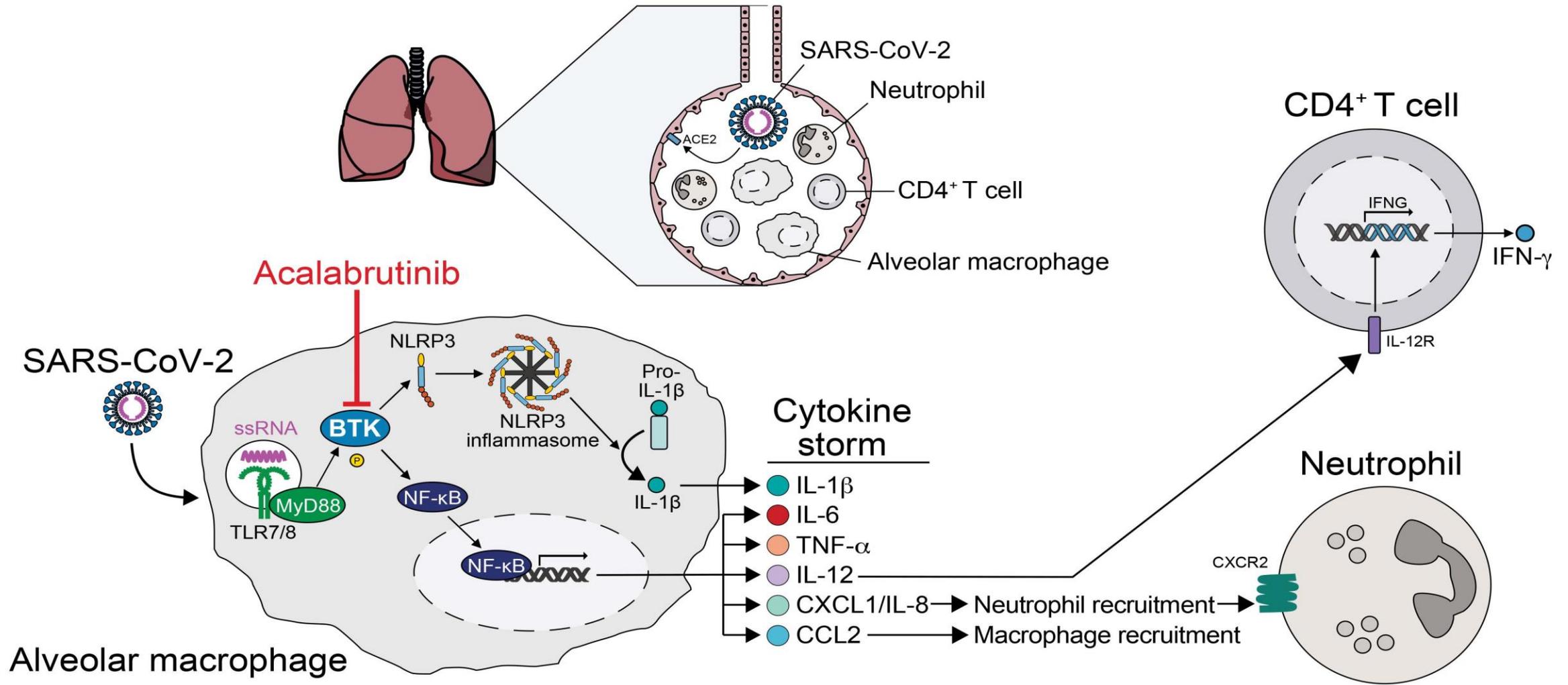


Study Imagined April 1, 2020
Study Activated May 21, 2020
220 sites registered as of June 2, 2020
1st patient enrolled June 5, 2020

Inhibition of Bruton Tyrosine Kinase in Patients with Severe COVID-19

Mark Roschewski*, Jeff P. Sharman*, Joseph Roswarski*,
Andre Goy, M. Andrew Monticelli, Michael Roshon,
Steven H. Wrzesinski, Jacob Collen, Ahmed Hamdy,
Raquel Izumi, Kevin K. Chung, George W. Wright,
Michail S. Lionakis, Jose Baselga,
Louis M. Staudt#, and Wyndham H. Wilson#

Model of the Hyperinflammatory Lung in Covid-19



Off-label Use of Acalabrutinib to Treat Severe COVID-19

Hypothesis

Acalabrutinib will block the inflammatory response associated with severe COVID-19 and reduce the need for mechanical ventilation and death.

Objective

Determine the safety and efficacy of acalabrutinib with best supportive care in hospitalized patients with moderate to severe COVID-19.

Endpoints

- Need for mechanical ventilation or death while hospitalized for COVID-19
- Overall safety profile of acalabrutinib in moderate to severe COVID-19.

Inclusion criteria

- Confirmed COVID-19 requiring hospitalization with at least 1 of the following:
 - Oxygen saturation of less than 94% on room air
 - Ferritin > 500 U/L
 - C-reactive protein (CRP) > 10 mg/dL

Off-label Use of Acalabrutinib to Treat Severe COVID-19

Case series (n=19):

- 11 patients on supplemental O₂ including high-flow nasal cannula
- 8 patients intubated and on mechanical ventilation

Treatment sites

- Hackensack University Medical Center (Hackensack, NJ) n=6
- Walter Reed National Military Medical Center (Bethesda, MD) n=4
- St. Francis Medical Center (Colorado Springs, CO) n=4
- Penrose Hospital (Colorado Springs, CO) n=3
- St. Peter's Hospital (Albany, NY) n=2

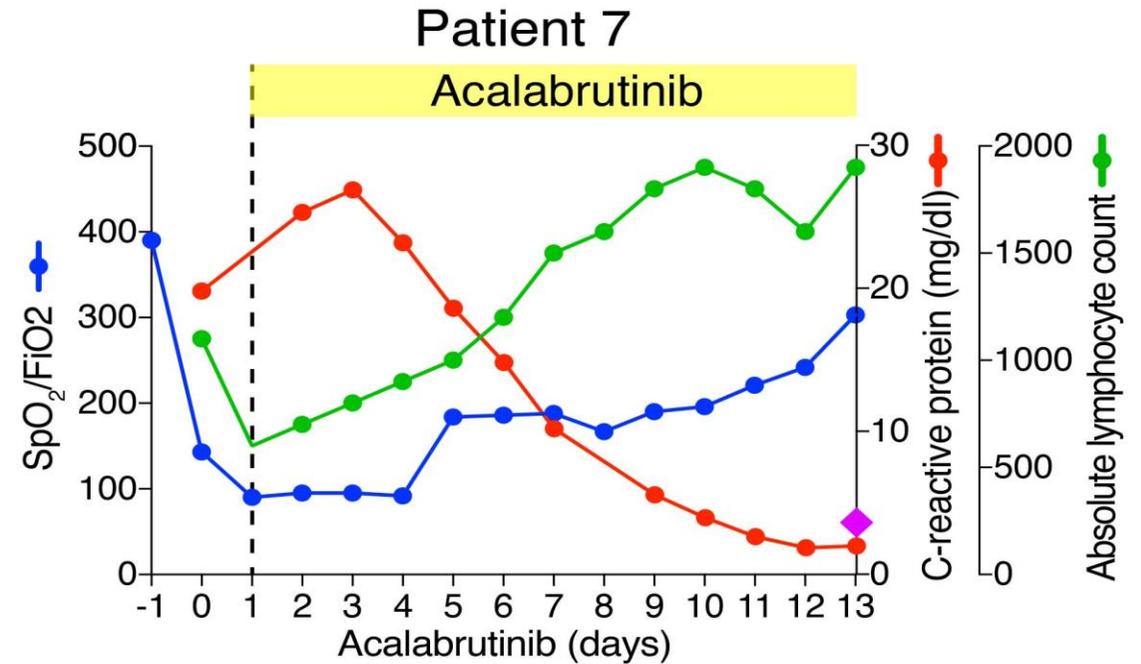
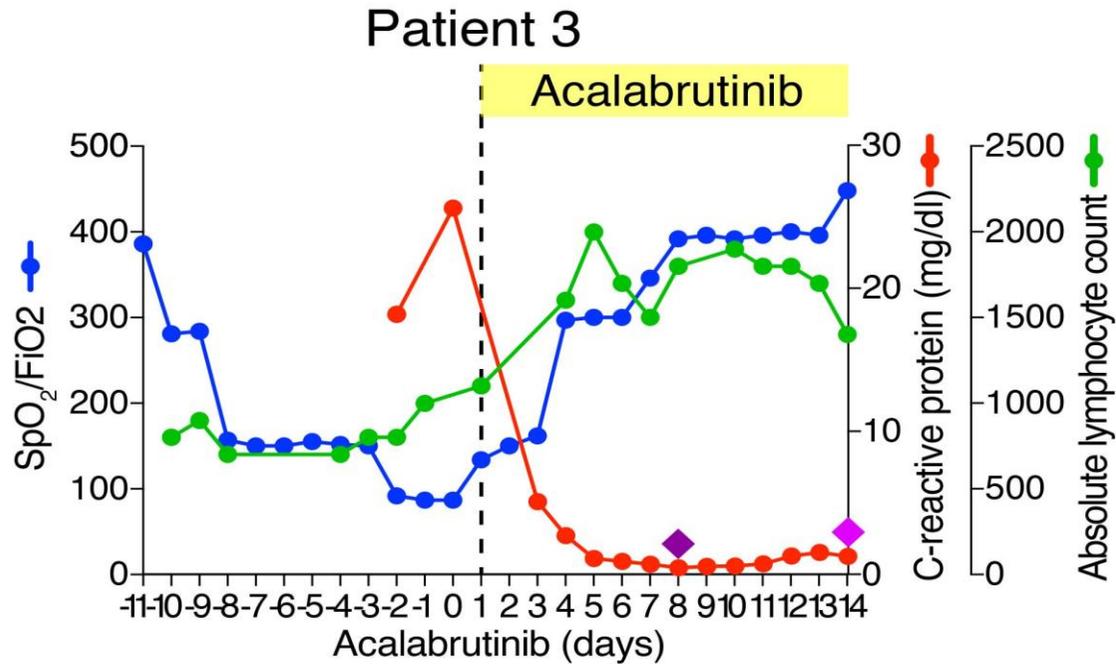
Design

- Acalabrutinib treatment (100 mg BID) for 10-14 days
- Monitor daily oxygen uptake (Blood O₂ saturation (%) / O₂ delivery (FiO₂)
- Assess inflammatory markers and clinical status throughout therapy

Correlative studies

- Correlates of COVID infection (absolute lymphocyte count)
- Correlates of inflammation (C-reactive protein, ferritin, D-dimer, fibrinogen)
- Cytokines (IL-6)

Acalabrutinib Blocks Inflammation and Reverses Severe COVID-19



- Blood oxygen saturation (%) / FiO₂
- ◆ Extubated
- C-reactive protein (mg/dl)
- ◆ Room air
- Blood absolute lymphocyte count (cells/ μ L)
- ◆ Discharged

BTK Inhibition in Severe COVID-19

- **Acalabrutinib treatments was associated with temporal improvement/ normalization of CRP, IL-6, lymphocyte count and oxygenation**
 - ✓ **Supplemental oxygen cohort:**
 - 9/11 discharged/room air from hospital
 - ✓ **Ventilator cohort:**
 - 4/8 extubated; 2 discharged; 1 on supplemental O₂; 1 death (PE)
 - ✓ **Safety:** No toxicity attributable to acalabrutinib
- **In vivo blood monocyte BTK activation and IL-6:**
 - ✓ Severe COVID-19 patients had increased activated BTK and IL-6 compared with controls
- **Monocyte activation may underlie the pathobiology of severe COVID-19**
 - ✓ “High” macrophage inflammatory “set point” associated with obesity, diabetes and/or hypertension may place patients at risk of COVID-19 inflammatory storm

Appreciation

Demonstrates the potential for NCI—working its grantees—to flexibly make use of its clinical research infrastructure in a time of national emergency

CTEP

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