Innovative Solutions.
Best Practices.
Excellence in Cancer Research.

Howard A. Burris, III, MD
Chief Medical Officer, Sarah Cannon

“Best management of any cancer patient is participation in a clinical trial”
NCCN Guidelines

MISSION:
People who live with cancer – those who work to prevent it, fight it, and survive it – are at the heart of every decision we make. Bringing the most innovative medical minds together with the most passionate caregivers in their communities, we are transforming care and personalizing treatment. Through clinical excellence and cutting edge research, Sarah Cannon is redefining cancer care around the world.

Research Sites

Strategic Sites
- Tennessee Oncology, Nashville
- Tennessee Oncology, Chattanooga
- Florida Cancer Specialists, West Palm Beach
- Florida Cancer Specialists, North, St. Petersburg
- Florida Cancer Specialists, Fort Lauderdale, Tallahassee, Orlando
- Oklahoma University, Oklahoma City
- HCA Midwest Health, Kansas City

DDU/Phase 1
- Tennessee Oncology, Nashville
- Florida Cancer Specialists, Sarasota
- Oklahoma University, Oklahoma City
- Sarah Cannon, London
- Sarah Cannon, Denver

Sarah Cannon BMT Programs
- Sarah Cannon Center for Blood Cancer, Nashville
- Colorado Blood Cancer Institute, Denver
- Texas Transplant Institute, San Antonio
- St. David’s South Austin Medical Center, Austin

INTERNATIONAL:
Central London

ASCO Research Community Forum
2018 Annual Meeting
Drug Development Program

- Tennessee Oncology Nashville 1998
- Florida Cancer Specialists Sarasota 2009
- Oklahoma Univ. Medical Center Oklahoma City 2009
- Sarah Cannon UK London 2010
- Sarah Cannon HealthONE Denver 2014

Research Highlights

- 3,000+ Patients enrolled in clinical trials per year
- 300+ First-in-human clinical trials conducted
- Participated in the development of 38 of 47 cancer compounds approved by the FDA in 2017.
- 5,000+ Patients enrolled in immunotherapy trials to date

Challenges in Clinical Research

- Data (volume, interpretation)
- Education
- Expansion cohorts
- Trial complexity
- Overwhelming paperwork
- Vast numbers of trials
- Rare mutations
- Eligibility criteria
- Patient access

Innovative Solutions

- Genospace and Molecular Cancer Conferences
NGS Testing - In the News

Two Trends, One Triage Decision

Precision Medicine

Immu-Oncology

NGS Profiling

Actionable Genomic Alterations

MSI and TMB

The Benefit of NGS Profiling:

- For the patient/individual benefit
- For clinical research/drug development (trial accrual)
- For cancer research/benefit of all (biology, resistance)
Correlation Between TMB and Response Rate to PD-1 Inhibition

The Challenge of Precision Medicine

The Larotrectinib Story (NTRK inhibitor)
Genospace: Enabling the Convergence of Clinical Research and Clinical Care

Large-scale clinical-genomic data aggregation

Clinical Decision Support

Data

WISDOM

Action

Insight

Discovery & Trial Recruitment

Genospace: Enabling the Convergence of Clinical Research and Clinical Care

LAUNCH - TOP ACTIONS IN GENOSPACE

Access by Use Case for Sarah Cannon Users

December 2017

Population Analytics

Clarify

Trial Coordinator

Single Patient View

Back-End Users: Genomics Team, Personalized Medicine Team, Super User Physicians, Development Innovations, Strategic Development

Front-End Users: Personalized Medicine Team, Research Nurses, Program Managers, Physicians
Molecular Tumor Board (aka: Molecular Cancer Conference)

- **Purpose:** To solely review molecular profiling data and provide guidance and education on:
  - Potential suitability of patients to clinical trial options
  - Potential suitability of patients to targeted therapies
  - Potential contraindications
  - Potential germline considerations
- **What we do not do:**
  - We do not take into consideration other clinical parameters that might otherwise influence patient eligibility for targeted therapies/clinical trials
  - We do not track slot availability of studies
  - We do not practice medicine – we give scientific rationale for why (or why not) a patient might be appropriate for specific study/therapy
- **We also highlight:**
  - Emerging mutation/molecule pairs (IDH/PARPi)
  - Emerging FDA approvals in oncology (Nivo in SCLC)
  - Uncommon genes with novel MOA implications (MTAP loss/MAT2A)
  - Emerging Personalized Medicine oncology related scientific data (from conferences and literature reviews)

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Molecular Cancer Conference: Data to Date

- Molecular profiling has increased since the inception of the Molecular Cancer Conferences.
- Physicians are profiling a wide range of tumor types.
- Over 18% of patients discussed at MCCs went on a clinical trial, and the majority of MCC patients went on targeted therapies.

- Molecular Profiles Ordered per Month:

<table>
<thead>
<tr>
<th>Month</th>
<th>Profiles Ordered</th>
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<tbody>
<tr>
<td>Jan</td>
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<td>Oct</td>
<td>40</td>
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<tr>
<td>Nov</td>
<td>30</td>
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<tr>
<td>Dec</td>
<td>20</td>
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</tbody>
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Molecular Cancer Conference – HNSCC with Guardant360 Testing

- Though the ERBB2 (HER2) mutations are classified as VUS and have not been biochemically characterized, there are studies accepting ERBB2 point mutations for HNSCC.
- Both HER2 mutations lie in the extracellular domain. V541M lies in a ligand binding site. Neither has been reported in COSMIC and response to inhibition is unknown.

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Trial Matching Benefits

The ability to harmonize disparate data sources and act upon this data is transformative by:
- empowering physicians to more confidently order molecular tests for patients
- democratizing access to cutting edge technologies for patients
- allowing matching of patients to appropriate trials at scale
**Best Practices**

Operational Excellence Initiatives

**KEYNOTE-001 Accelerated Approval**
- ORR 19.4%; OS 12 mos
- ORR 33%; OS 23 mos
- FIH trial initiated January 2011
- Breakthrough therapy designation
- September 2014 Melanoma Approval
- October 2015 NSCLC Approval

**Seamless Oncology Drug Development**

Given the potential for greater efficiency afforded by seamless expansion-cohort designs and the potential risks involved in such trials, additional patient safeguards are necessary. We propose that the FDA's "breakthrough therapy" designation be considered as a mechanism of identifying drugs with sufficient early evidence of efficacy to justify a seamless development program.

Prowell et al. NEJM May 26, 2016

**Expansion Cohort Challenges**

- Line of therapy (early versus refractory)
- Commercial drug versus clinical trial competition
- Blood versus solid
- Specific diseases or genomic mutations
- Different referral sources
- Disease management expertise
- Study procedures (DDU/Ph1 capability)
- Consents

FDA Draft Guidance August 2018: Expansion Cohorts in FIH Trials to Expedite Development

- Definition: 3 or more additional patient cohorts with cohort specific objectives (i.e., efficacy, expanded safety, alternative regimens, combinations, biomarker value)
- Risks: disseminating new information; exposing large numbers of patients to suboptimal or toxic doses; misinterpreting results/unplanned comparisons
- Benefits must outweigh risks; serious diseases with no curative therapy

Each cohort must have scientific rationale and firm objectives/endpoints
- Generally 40 solid tumor or 20 hematologic malignancy patients/cohort
- Strongly consider pediatric cohort
- Communication plan for safety updates (FDA, IRB, sites)
- Independent Safety Assessment Committee (ISAC) or Independent Data Monitoring Committee (IDMC)
- Central IRB recommended
- Amendment/consent submitted to FDA 30 days before planned activation

Over 66% of our studies have more than one arm...
BMS Fraction Program

Following the Patient Experience with Innovative Clinical Trial Design — The FRACTION™ Program

- Patients with advanced NSCLC (squamous & non-squamous)
- Innovative and Efficient Trial Design
- Innovative design to efficiently evaluate I-O combos for delivery of transformational effects
- Ability to explore potential benefits across range of patients
- New investigational treatments administered based on patient response

Trial Complexity

- 55% of current protocols at Sarah Cannon are considered “high” complexity based on weighting tool which factors intensity from procedures, schedule, visit volume, and data requirements
- Numerous sample collection procedures (apheresis, tissue, blood, stool, etc.)
- Multiple committee approvals (IRB, IBC, hospital review board, etc.)
- Intensive support/monitoring (1:1 nursing; CRS management; overnight hospitalization)
- Complex drug administration (intratumoral injection, oncolytic viruses, neoantigen vaccines, etc.)

Protocol Weighting Tool Example

<table>
<thead>
<tr>
<th>Protocol Weighting Tool Example</th>
<th>ASCO Research Community Forum Annual Meeting</th>
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</thead>
</table>

Clinical Operations & Site Management Organization

- Clinical Trial Pipeline
- Regulatory
- Safety
- Contracting & Budget Services
- Site Development & Management

ASCO Research Community Forum Annual Meeting
**Investment in Systems**

Invested heavily in systems to aid in execution of increasingly complex trials...

- **E-Signature**
  - Route and execute documents

- **Document Management**
  - Post and access patient files

- **Molecular Profiling**
  - Match patients to open trials based on genetic testing

- **Electronic Medical Record**
  - Capture patient visit information

- **Clinical Trial Management**
  - Manage patient visit entry and billing

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**Operational Excellence: Service Offering**

**OBJECTIVE**
- Determine project viability and define manageable project scope

**FOCUS**
- Scope

**RESOURCE NEEDS**
- Subject matter experts from impacted functional areas

**USE WHEN**
- Aware of a problem but unclear where to focus for improvements
- Efficiency idea or hypothesis but need data to validate if it is worth pursuing

**DELIVERABLES**
- Statement of Work (SOW) for each proposed project
- Summary business case
- Detailed, integrated implementation plan
- Supporting materials
- Value proposition, if needed

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**Operational Excellence: Recent Projects**

1. **UNAPPLIED CASH**
   - What are the process problems contributing to the growing unapplied cash balance?

2. **AMENDMENT VOLUME**
   - How has amendment volume changed, and what processes does it affect?

3. **ARM MANAGEMENT**
   - How can we improve the management and communication around arm availability to better inform our system builds?
Data Complexities and Financial Impact in Clinical Research

Development of Contract Modeling Team

- **Overview**
  - Team was developed out of necessity due to gaps in data and resulting financial impacts
  - Tracking tools and templates to recover underreported data/revenue due to complexities

- **Site Partnership and Revenue Assurance**
  - 18% of data was recognized > 1 month late in 2017
  - Additional data underreported and “missing”
  - Secondary goal of reducing Unapplied Cash, as data in EDC must match data invoiced to Sponsor

- **Centralized Gatekeeper of All Data and Financial Activity**

- **Analytical Tools**
  - Missing Visits Report
    - Automated CTMS report to identify data gaps based on Protocol Schedule and Visit Windows
  - Activity and Revenue Templates

- **Systems Implementation**
  - Future integration of all systems for centralized data source and single entry

Clinical Trial Budget Approval— High vs Low External Charges

<table>
<thead>
<tr>
<th>Internal Procedure Charges</th>
<th>External Procedure Charges</th>
<th>Staff Time Charges</th>
</tr>
</thead>
<tbody>
<tr>
<td>$10,150, 49%</td>
<td>$6,230, 30%</td>
<td>$4,328, 21%</td>
</tr>
<tr>
<td>$11,088, 52%</td>
<td>$8,756, 41%</td>
<td>$1,499, 7%</td>
</tr>
<tr>
<td>$1,490, 1%</td>
<td>$6,008, 52%</td>
<td></td>
</tr>
</tbody>
</table>

Amendment Volume

Amendment volume continues to grow...

- 33% of amendments include design changes (added arms, cohorts, etc.)
- 10 sponsors account for 42% of amendment volume

Amendment Inbox

- Own receipt and dissemination of amendments prior to IRB approval.
- Track incoming amendments in CTMS.
  - Volume: YTD : 747
  - Monthly Average : 107

ASCO Research Community Forum Annual Meeting
2018 Annual Meeting
Amendment Costs

- Financial (tracking, billing per procedure)
- Training and education (MDs, RNs, staff)
- Consents (time, IRB, tracking, reconsenting)

INDSR Reporting Statistics

Safety Letter Volume
- 120,000 letters received 10/20/18
- 50,000 single pharma sponsor (45,000 single IO agent)
- 10,000 each from three additional sponsors

Sarah Cannon’s e-Reg Binder

Excellence in Cancer Research

PRIMER, BASKET and UMBRELLA Trials
**PRiMER Program**

**Recent Observations:**
- Early phase studies are growing larger, with expansion cohorts that replace the traditional "phase 2" study.
- Many of the expansion cohorts are enrolling rare tumor types, or patients with minimally (or even untreated) disease.
- Multi-histology studies are becoming increasingly common.

**Our Objectives:**
- To allow more patients and treating physicians access to exciting clinical trials by bringing earlier phase research and novel trial designs to the traditional "late phase" clinics
- To contribute to accelerated drug development by opening large expansion cohorts in the clinics where the patients are being seen

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**Types of Trials in the PRiMER Program**

- Phase 2/3 studies driven by profiling or that include a number of tumor types (PRO, MULTI)
- Bridge trials that either open in the DDU and expand to Bridge, or open initially at Bridge Clinics
- Phase 1b trials or phase 1 trials with dose-finding cohorts that can be open in our late phase clinics
- Studies that begin as single tumor type trials but evolve to include other tumor types (MULTI)

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**Table 1. Types of Master Protocols.**

<table>
<thead>
<tr>
<th>Type of Trial</th>
<th>Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Umbrella</td>
<td>To study multiple targeted therapies in the context of a single disease</td>
</tr>
<tr>
<td>Basket</td>
<td>To study a single targeted therapy in the context of multiple diseases or disease subtypes</td>
</tr>
<tr>
<td>Platform</td>
<td>To study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm</td>
</tr>
</tbody>
</table>

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**PRiMER Program: Study Expansion Considerations**

- **PK and other lab requirements**
  - Length of PK days
  - Frequency of lab collections
  - Processing requirements (e.g. refrigerated centrifuge, freezer capabilities)

- **Adverse event management**
  - Patient evaluable
  - Dose limiting toxicities (DLTs)
  - Sibling cohort management
  - Experience with this drug or similar MOA

- **Pharmacy considerations**
  - Drug stability
  - Drug preparation and administration

- **Sponsor commitments**
  - Weekly or biweekly teleconferences
  - Slot/cohort management
  - Frequency and volume of data collection

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**Cross-functional evaluation of study expansion**

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Woodcock J and LaVange LM. NEJM 2017;377:62-70
Next Generation Genomic Trial Designs

ASCO TAPUR Study: Targeted Agent and Profiling Utilization Registry

<table>
<thead>
<tr>
<th>Drug 1</th>
<th>Drug 2</th>
<th>Drug 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib</td>
<td>Temsirolimus</td>
<td>Regorafenib</td>
</tr>
<tr>
<td>Axitinib</td>
<td>Trastuzumab + Pertuzumab</td>
<td>Olaparib</td>
</tr>
<tr>
<td>Bosutinib</td>
<td>Vemurafenib + Cobimetinib</td>
<td>Pembrolizumab</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>Vismodegib</td>
<td>Nivolumab + Ipilimumab</td>
</tr>
<tr>
<td>Palbociclib</td>
<td>Cetuximab</td>
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<tr>
<td>Sunitinib</td>
<td>Dasatinib</td>
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</tbody>
</table>

MyPathway: Study Design

MyPathway Basket Trial Preliminary Results

HER2 Colorectal
- 38% ORR

HER2 Bladder
- 33% ORR

HER2 Biliary
- 29% ORR

BRAF NSCLC
- 43% ORR
**Takeaways**

- Clinical Research is absolutely vital; “If not us, then who?”
- Investments in systems and processes is critical
- No money, no mission

“Caring for every patient, learning from every patient”