Carolina BioOncology Institute
CANCER RESEARCH CLINIC

Early Phase Clinical Trials

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September 26th 2025

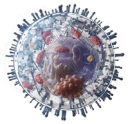
Conflict of Interest Disclosures for Neel Gandhi MD

Developing Intellectual Property for CBOI & BioCytics

Perform clinical trials and/or consulting for AbbVie, Apollo, Acrivon, Arvinas, BioNTech, Brightpeak, Cytomx, EMD Serono, Ensem, Exelixis, Instil Bio, Dren Bio, GI Innovation, Multitude,Nuvation Bio, Qurgen, Revolution Medicines, Teva, Terremoto.

“Cancer is an expansionist disease; it invades through tissues, sets up colonies in hostile landscapes, seeking “sanctuary” in one organ and then immigrating to another. It lives desperately, inventively, fiercely, territorially, cannily, and defensively—at times, as if teaching us how to survive. To confront cancer is to encounter a parallel species, one perhaps more adapted to survival than even we are.”

Siddharta Mukherjee M.D, Emperor of Maladies.



Treating Cancer in the Past

Evolution of Cancer Therapy

Discovery of taxanes, platinum agents, combination chemotherapy regimens

1940

Targeted Therapy: Gefinitib and Erlotinib for EGFR mutation positive NSCLC

2003

Checkpoint Inhibitors

2011

Cell Therapy Cancer Vaccines

2025

Father of Modern Day Chemotherapy

Immunotherapy Era

Why Pursue Clinical Trials?

- Access to the latest cancer treatments in research **before FDA approval**
- **Contributing to advancement** of cancer therapies for future patients
- Offer **hope**, especially when standard treatment options are limited

U.S. Food and Drug Administration

Drug Approval Process

What is a drug as defined by the FDA?

A drug is any product that is intended for use in the diagnosis, cure mitigation, treatment , or prevention of disease; and that tis intended to affect the structure or any function of the body.

PRE-CLINICAL

Drug Sponsor's Discovery and Screening Phase

Drug Developed

Drug sponsor develops a new drug compound and seeks to have it approved by FDA for sale in the United States.

1

Animals Tested

Sponsor must test new drug on animals for toxicity. Multiple species are used to gather basic information on the safety and efficacy of the compound being investigated/researched.

2

IND Application

The sponsor submits an Investigational New Drug (IND) application to FDA based on the results from intial testing that include, the drug's composition and manufacturing, and develops a plan for testing the drug on humans.

IND REVIEW

FDA reviews the IND to assure that the proposed studies, generally referred to as clinical trials, do not place human subjects at unreasonable risk of harm. FDA also verifies that there are adequate informed consent and human subject protection.

FDA's Center for Drug Evaluation and Research (CDER) evaluates new drugs before they can be sold.

The center's evaluation not only prevents quackery, but also provides doctors and patients the information they need to use medicines wisely. CDER ensures that drugs, both brand-name and generic, are effective and their health benefits outweigh their known risks.

CLINICAL

Drug Sponsor's Clinical Studies/Trials

3

PHASE 1

20-80

The typical number of healthy volunteers used in Phase 1; this phase emphasizes safety. The goal here in this phase is to determine what the drug's most frequent side effects are and, often, how the drug is metabolized and excreted.

4

PHASE 2

100's

The typical number of patients used in Phase 2; this phase emphasizes effectiveness. This goal is to obtain preliminary data on whether the drug works in people who have a certain disease or condition. For controlled trials, patients receiving the drug are compared with similar patients receiving a different treatment--usually a placebo, or a different drug. Safety continues to be evaluated, and short-term side effects are studied.

At the end of Phase 2, FDA and sponsors discuss how large-scale studies in Phase 3 will be done.

5

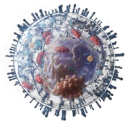
PHASE 3

1000's

The typical number of patients used in Phase 3. These studies gather more information about safety and effectiveness, study different populations and different dosages, and uses the drug in combination with other drugs.

General Overview of Trial phases

- **Phase 1 trials**: Evaluate safety
  - First-in-human (Biotech/Pharma Driven)
  - Investigator Initiated (Repurposed drugs)
- **Phase 2 trials**: Evaluate efficacy
  - Single arm vs. randomized in specific tumor types
- **Phase 3 trials**: Evaluate treatment arm in comparison to standard of care (Randomized)
- **Phase 4 trials**: Post-marketing



When to pursue which trials?

- Phase 3 trials often pursued as first line treatment (i.e. treatment before or after surgery, first line metastatic disease)
  - **Overall Survival** key metric
  - Large, international studies at hospital systems and academic centers

- Phase 1/2 trials often pursued for treatment in metastatic setting (second line, third line, or beyond)
  - Progression Free Survival, Response Rate, Safety Data
  - Limited to Early Phase Trial Clinics and academic centers
  - **Becoming more popular due to cancer advances**

Balancing Therapeutic Intent & (Mis)conception for Phase 1 trials

- Primary objectives of phase 1 trial is to assess safety and toxicity. Secondary objective is to determine if anti-tumor effect
- Physician/Investigators' have "therapeutic intent to aim at the druggable target" because modern drugs are highly engineered for this purpose
- Patients' (mis)conception is they might be receiving an effective therapy (or may not benefit at all)
- ASCO's position is that phase 1 trials have the potential to provide patients with clinical benefit.

Source: Correcting ASCO Position on Phase 1 Clinical Trials in Cancer, H Burris, Nature Reviews, Clinical Oncology, 2020; https://www.nature.com/articles/s41571-019-0311-4
Phase 1 Trials as Valid Therapeutic Options for Patients with Cancer, J Adashek et al; Nature Reviews, Clinical Oncology, 2019; https://www.nature.com/articles/s41571-019-0262-9

Phase 1 Trials are Valid Therapeutic Options for Patients with Cancer

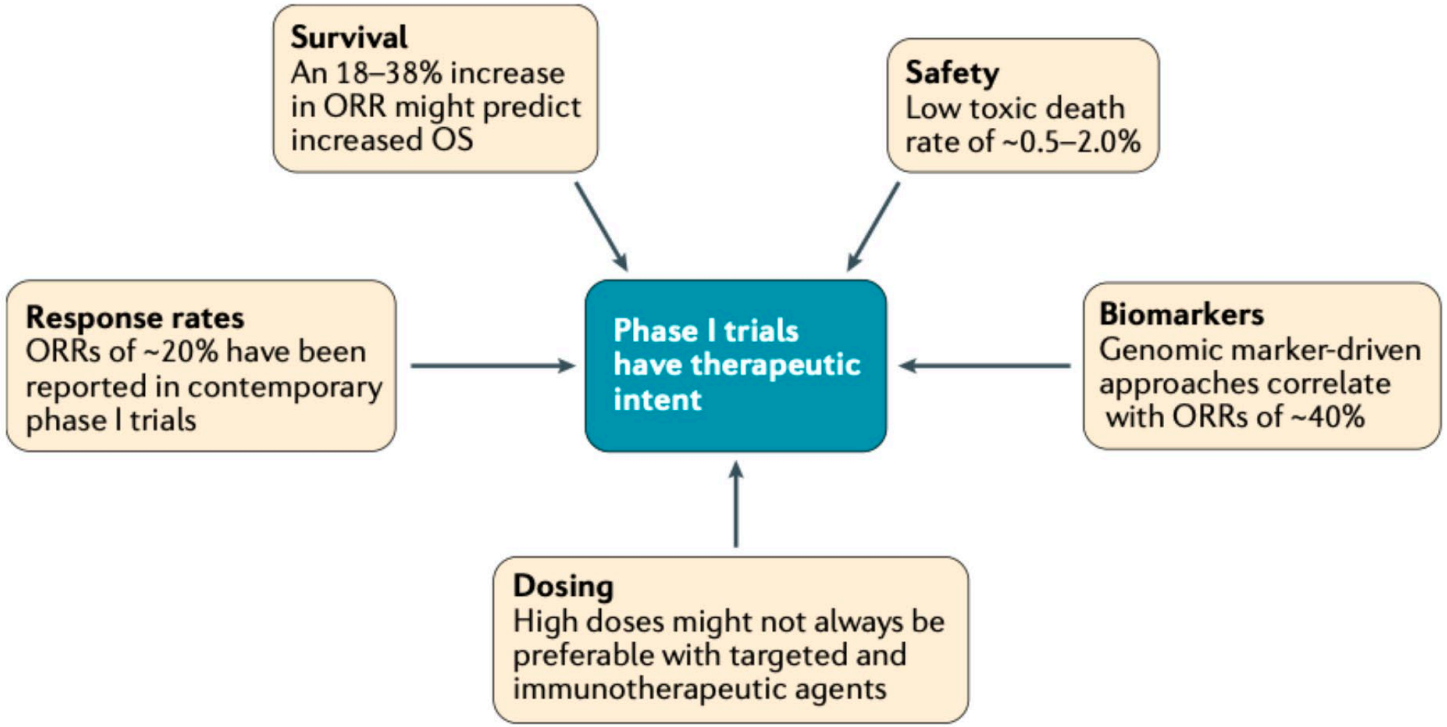
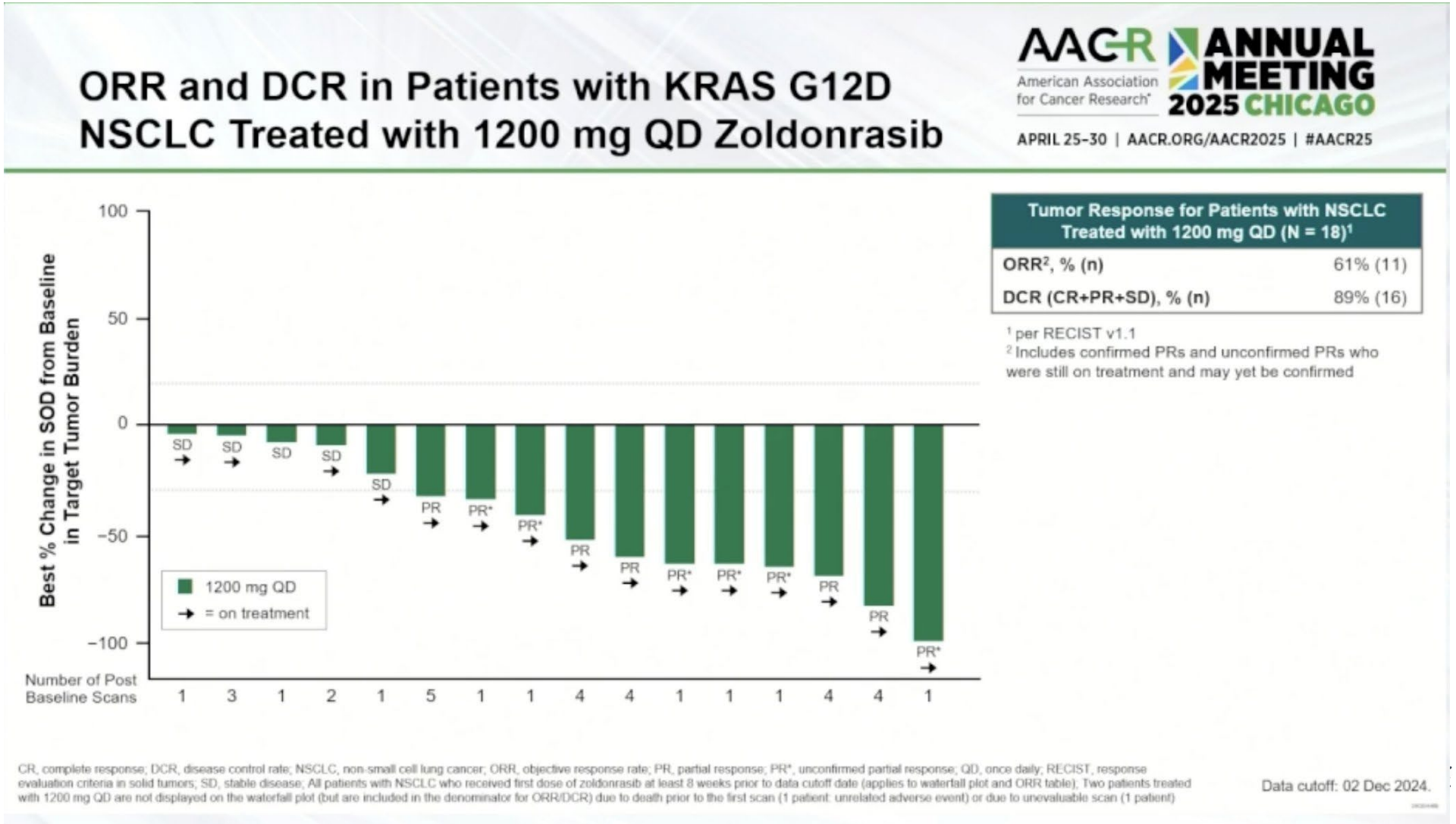


Fig. 1 | **Phase I trials as valid therapeutic options.** The design adaptations made in phase I trials in the past few years (in aspects including dosing[63], biomarkers[8,9,17,30,56,70], safety[14], survival[71] and responses[18]) have helped them to become valid therapeutic options. We propose that researchers can anticipate therapeutic responses in contemporary phase I trials and therefore these trials can be considered to have therapeutic intent.

Source:
Phase 1 Trials as Valid Therapeutic Options for Patients with Cancer, J Adashek et al; Nature Reviews, Clinical Oncology, 2019; https://www.nature.com/articles/s41571-019-0262-9

When to consider Phase 1/Phase 2 trials for lung cancer?

- If next gene sequencing test links to an **actionable mutation** without FDA approved treatments



When to consider Phase 1/Phase 2 trials for lung cancer?

- When standard treatments fail:
  - Extensive research being conducted on overcoming **immunotherapy resistance**
    - **Combining PD1 antibodies with novel immuno-stimulants**
    - **Bispecific antibodies**
  - Identifying novel targets expressed on surface of cancer cell (cMet, etc)
    - **Antibody Drug Conjugates (“Chemo on a stick”)**
- ***PD1 negative and without actionable mutations***

Phase 1 Trials for Lung Cancer at CBOI

- XB628-01 (Sponsor Exelixis) with **XB628** (NKG2A/PDL1 Bispecific Ab, with modified inactive Fc function). **PI: Neel Gandhi M.D**. https://www.clinicaltrials.gov/study/NCT06952010

- CP-AU-007-01 (Sponsor Aulos) with **AU-007** (mAb binds to IL-2 and inhibits IL-2Ra binding) + Aldesleukin + Avelumab. Potentiating IL-2. **John Powderly M.D**. https://www.clinicaltrials.gov/study/NCT05267626

- XB010-101 (Sponsor Exelixis) with **XB010** (anti-5T4 IgG1 Ab conjugated to MMAE) **+/- Pembrolizumab**. **PI: John Powderly M.D**. https://www.clinicaltrials.gov/study/NCT06545331

- ACR-2316-101 (Sponsor Acrivon) with **ACR-2316** (WEE1/PKMYT1 oral small molecule inhibitor). **PI: Neel Gandhi M.D**. https://clinicaltrials.gov/study/NCT06667141

Trial Eligibility Checklist

- Good organ function
- Good performance status
- Good social support system
- Specific Trial Requirements: (pre-trial biopsy, avoid prohibited meds, etc)
- Can sometimes take 2-3 weeks to enroll onto a trial (consent, screening)

Trial Eligibility Checklist

- Brain metastasis (common in advanced lung cancer) need to be **treated** and **“stable”**
  - Modern stereotactic radiosurgery techniques employed
  - Modern trial drugs can cross blood brain barrier

Consider Phase 1/Phase 2 Trials Early!

- Always know about your options, even while on frontline standard treatments
- Waiting to enroll on a trial too late translates to poor outcomes

Trial Safety

- Because treatments are investigational, **frequent clinical assessments required**
- All potential side effects unknown, but can predict side effects based on class of drug
- Required to report all **serious adverse events (SAE) to FDA**

Financial Cost?

- Early phase trials not usually covered by insurance (bulk of costs covered by Sponsor), but this is changing
- Cost of traveling to clinic, lodging, and general impact on schedule
- Many funding sources available

Other Barriers

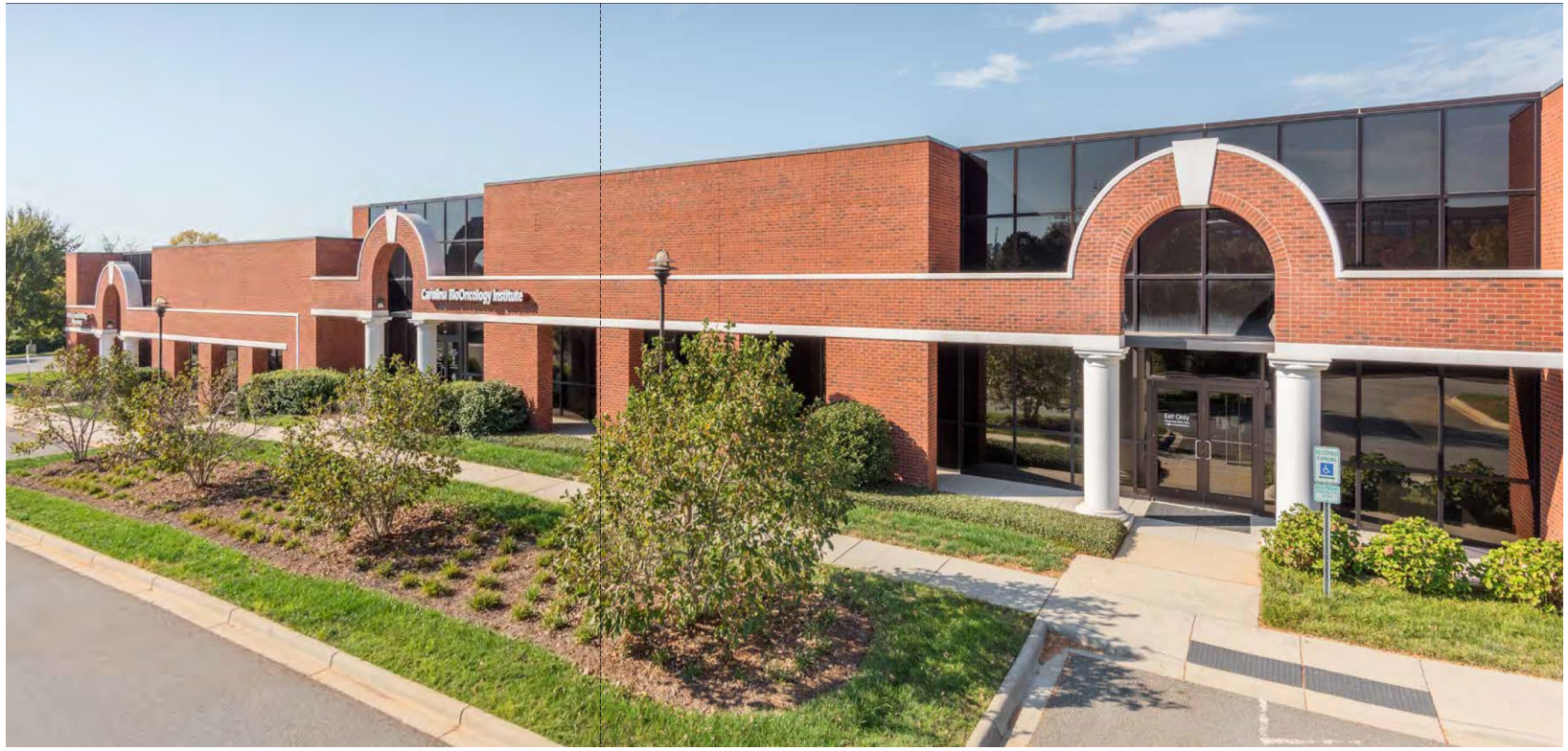
- Early phase trials often have strict eligibility (driven by Industry Sponsor/FDA requirements)
  - Big push to broaden eligibility so all patients can participate
- Hard to find the right trial!
  - Patients should be open minded about various options
  - AI algorithms (www.massivebio.com) can help locate specific trials
- Hard to secure a trial slot
  - Need integrated trial networks and centralized communication

Carolina BioOncology Institute
CANCER RESEARCH CLINIC

BioCytics
HUMAN APPLICATIONS LABORATORY

- PLLC, incorporated in North Carolina
  - Practices medicine, licensed by NC Med Board
  - Seen > 5,000 patients since founded
  - Opened > 160 phase 1 trials

- C-corp, incorporated in Delaware
  - “Living Cells, Applications of”
  - Holds intellectual property of cellular therapy R&D pipeline

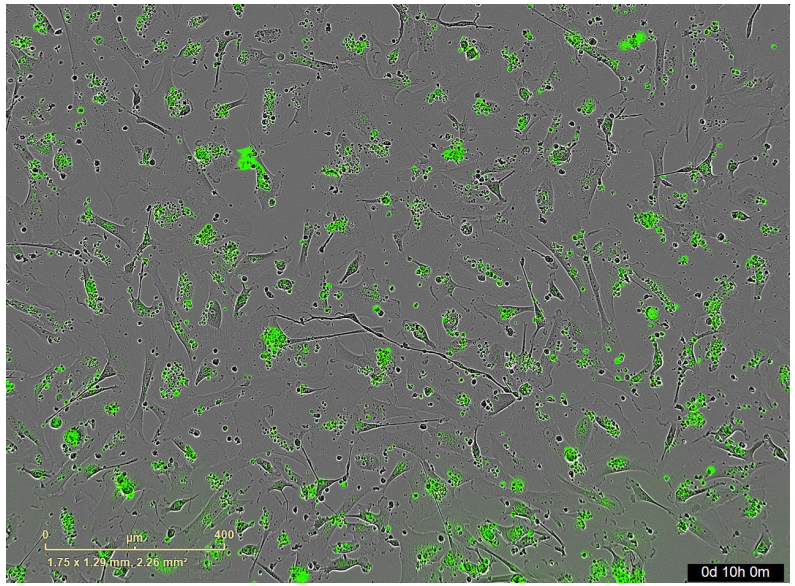


Both companies founded in 2005 by John Powderly MD, as reflections of the same vision

Our clinic

- Only U.S. privately held phase I clinic & Human Applications Lab

Only clinic in U.S. where a patient can see a T-Cell Factory from their infusion chair window.



Only clinic where a patient can see a video of how their own T cells kill their own cancer. “Battlefield”

The only hallway in U.S. that can walk a warm leukapheresis product directly into culture and dose the next week.

CBOI Immuno-Oncology Phase I Clinical Trial Site

Dedicated Phase I I/O community-based site:

- Highly trained, experienced & certified staff well versed in managing complexities of Phase I trial design & irAE management
- PI & CRC responsiveness
- Enables sponsor remote monitoring
- On site USP 797/800 pharmacy & GMP clean rooms steps away from infusion room
- Onsite high complexity CLIA certified clinical lab

Accelerated Start-up Timelines:

- Frequently the first site opened & 1572 submission site
- Trial start-up timelines are shorter, ~3-4 wks
- No local IRB or internal committee approvals needed

Access to Eligible Patients:

- Active wait list of patients pre-screened for trial readiness
- Daily referral from regional and local institutions

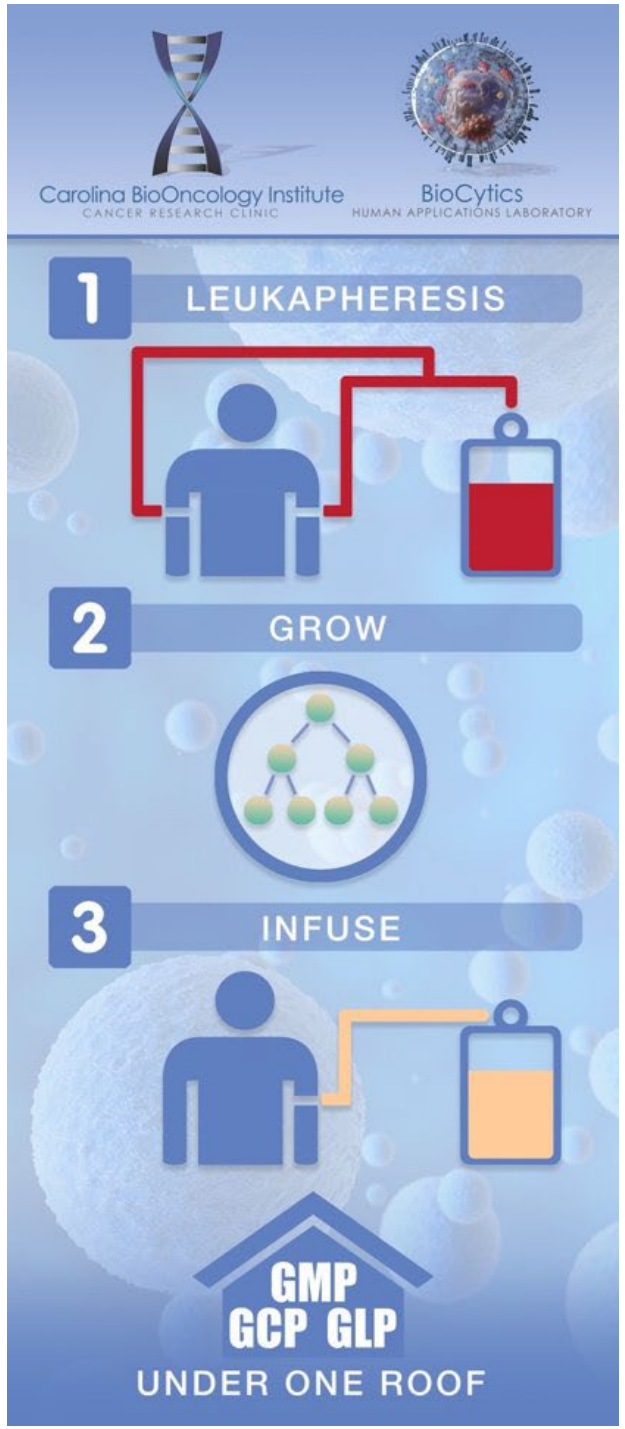
Data Timelines:

- 1-3 business day standard for data entry and query resolution

CBOI Immuno-Oncology Phase I Clinical Trial Site

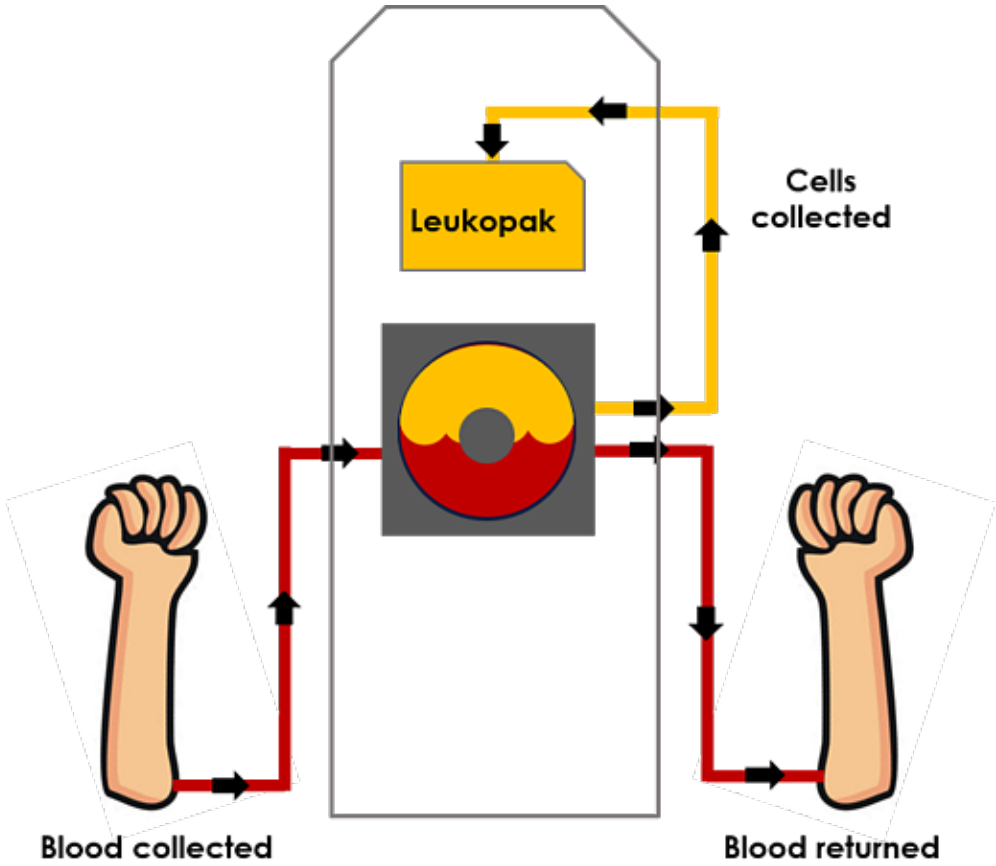
- Stage IV cancer patients referred from primary medical oncology (preferably early in treatment course, 1st or 2nd line of therapy)
- Treatment plan is formulated, and primary medical oncology team remains involved
- Trials are done with emphasis on patient safety, and all data reported to FDA

Our vision: Under one roof



Biocytics 0001: In-House Research

- Allows for the in-house collection and processing of patient tumor cells and immune cells.
- Different methods of collection:
  - Biopsy
  - Pleural effusion/ascites
  - Whole blood collections
  - Leukapheresis ***
- Non-therapeutic research, at this time.
- Volunteers welcome! This will help further our research to ultimately have a personalized option for cancer patients



https://www.caltagmedsystems.co.uk/information/what-is-leukapheresis/

Clinical Trial Volunteers are Heroes

Thank you from the Carolina Bio-Oncology Institute!