DANA-FARBER CANCER INSTITUTE

BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL

Clinical Trials 101

Eric Jacobsen, MD

Assistant Professor of Medicine

Harvard Medical School

Types of treatments

- **Chemotherapy**: typically kills cells by damaging DNA, preventing DNA synthesis, blocking cell division, or disrupting metabolism
- **Immunotherapy**: directly or indirectly uses immune system to kill cells (antibodies, vaccines, CAR-T cells)
- **Targeted therapies**: blocks a specific cell signaling pathway (vemurafenib, cobimetinib)
- **Gene therapy**: replace a damaged gene (CRISPR)

Benefits of clinical trials

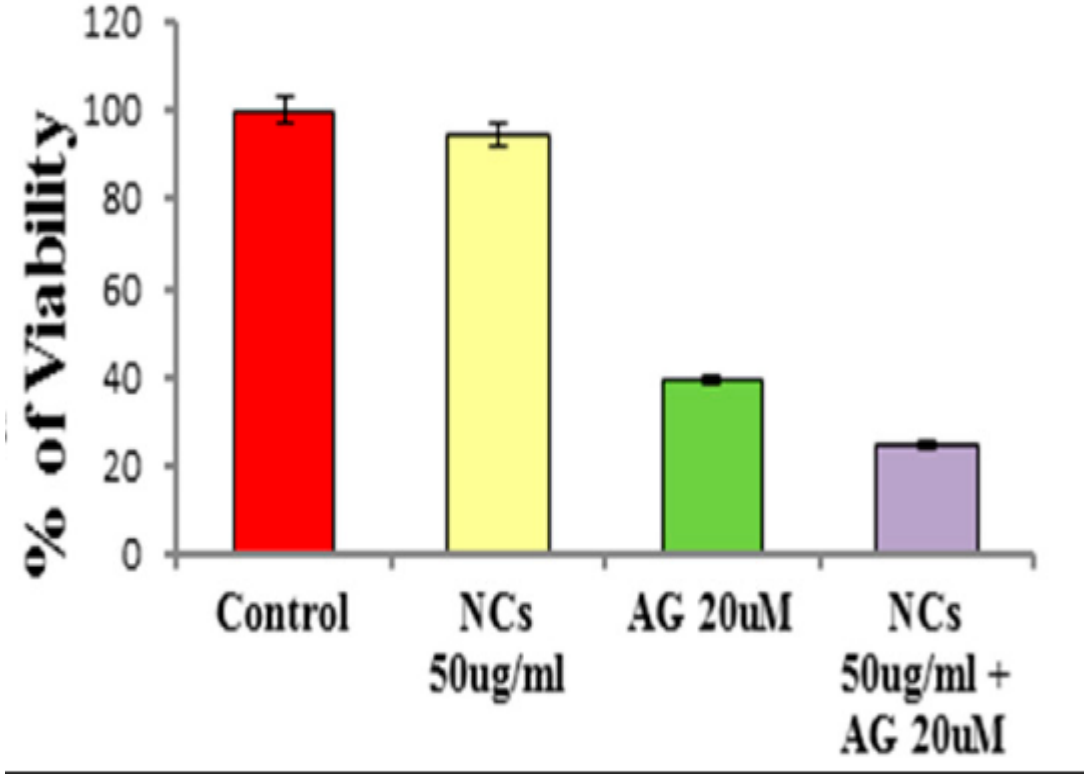
- Access to new medications
- Some studies show better outcomes in patients treated on clinical trials
- Improve scientific knowledge
- Altruism

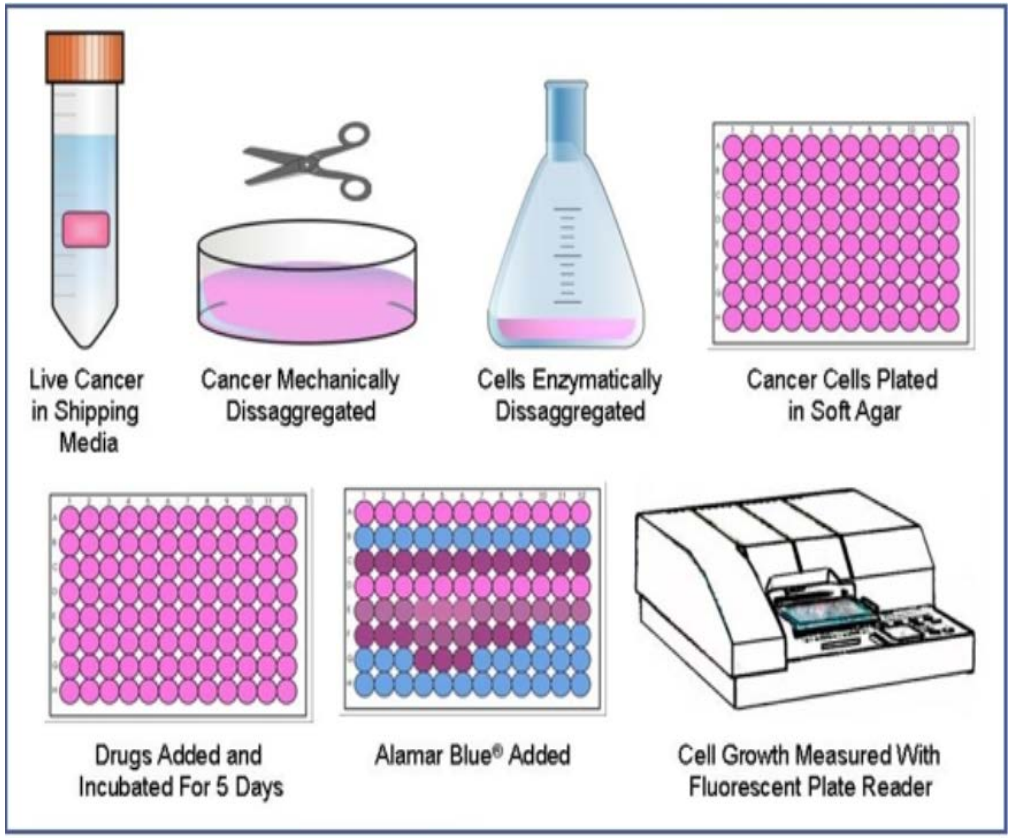
Only about 5% of adult cancer patients participate in clinical trials

Patient concerns about clinical trials

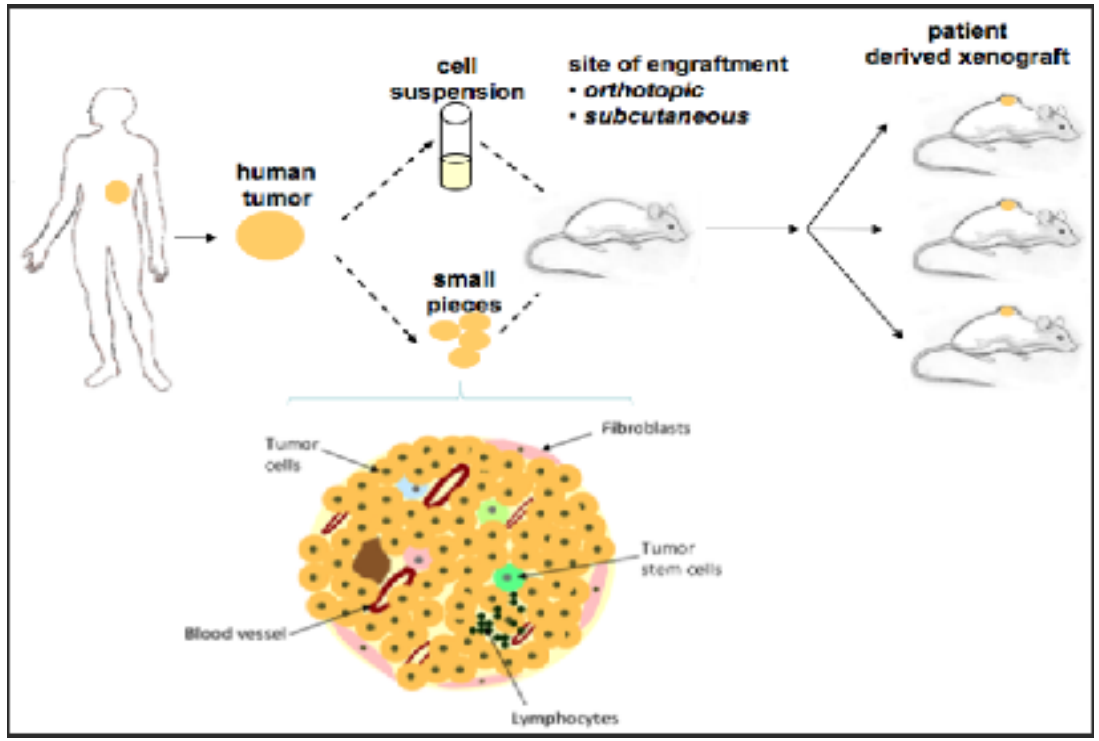
- "I don't want to be a guinea pig"
- I don't want a placebo
- Travel
- Cost
- More visits, more scans
- Less scheduling flexibility
- Loss of autonomy
- **Unknowns: effectiveness, side effects**

Pre-clinical testing – reducing uncertainty





Xenografts



PROXE

Phases of Clinical Trials

- **Phase I**: primary purpose is to assess safety, find optimal dose
- **Phase II**: larger trial to assess efficacy, expanded assessment of safety
- **Phase III**: typically compares new treatment to established standard (often randomized)
- **Phase IV**: post-marketing surveillance
- **Registries**

Process for initiating a trial

- Submit a letter of intent (LOI) or grant application
- Reviewed by funding source
- Concept review
- Write full protocol and consent form
- Scientific Review Committee, Institutional Review Board
- Activation
- Enrollment and data collection
- Publication

Metrics of success

- Historically in cancer studies we have focused on response rates, length of remission

- Increasing emphasis on symptom improvement, quality of life, resource utilization

FDA Approval Process

- Historical average: 12 years, $350-800 million
- 3.5 years of preclinical testing (999/1000 end here)
- Phase I testing: 1 year
- Phase II: 2 years
- Phase III: 3 years
- Application (100,000 pages): 2.5 years

Source: Drugs.com

Other ways to gain access to medications

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 5.2018
Diffuse Large B-Cell Lymphoma

NCCN Guidelines Index
Table of Contents
Discussion

STAGE

FIRST-LINE THERAPY[n]

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

Stage I, II[j,k]

- **Nonbulky (<7.5 cm)** → RCHOP[o] x 3 cycles followed by RT[p] (category 1) or RCHOP[o] x 6 cycles ± RT[p,q] or RCHOP-14 x 4–6 cycles ± RT[p,q]
- **Bulky (≥7.5 cm)** → RCHOP[o] x 6 cycles ± RT[p,q]

→ **RT planned** → See Pre RT Evaluation (BCEL-4)

→ **RT not planned** → See End-of-Treatment Restaging (BCEL-5)

Stage III, IV[j,l,m] → Clinical trial or RCHOP[o,r] (category 1)[s] → **Interim restaging after 2–4 cycles[t]** → See BCEL-6

[j]In testicular lymphoma, after completion of chemotherapy, scrotal RT should be given (25–30 Gy).
[k]In patients who are not candidates for chemotherapy, involved-site radiation therapy (ISRT) is recommended.
[l]In selected cases (4–6 factors according to prognostic model, HIV lymphoma, testicular, double hit lymphoma), there may be an increased risk of CNS events. The optimal management of these events is uncertain, but CNS prophylaxis can be considered with 4–8 doses of intrathecal methotrexate and/or cytarabine, or systemic methotrexate (3–3.5 g/m²) during the course of treatment. Recent data regarding stage IE DLBCL of the breast have been suggested as a potential risk for CNS disease. See Prognostic Model to Assess the Risk of CNS Disease (BCEL-A 2 of 2).
[m]For systemic disease with concurrent CNS disease, see BCEL-C.
[n]Recommendations are for HIV-negative lymphoma only. For HIV-positive DLBCL, see AIDS-2.

[o]See BCEL-C for regimens used in patients with poor left ventricular function and patients >80 years of age with comorbidities.
[p]See Principles of Radiation Therapy (NHODG-D).
[q]If RT is not used, interim staging after 3–4 cycles of RCHOP is appropriate to confirm response.
[r]Based on current clinical trials, RCHOP is preferable due to reduced toxicities, but other comparable anthracycline-based regimens are also acceptable (see BCEL-C).
[s]In selected cases, RT to initially bulky sites of disease may be beneficial (category 2B).
[t]PET/CT scan at interim restaging can lead to increased false positives and should be carefully considered in select cases. If PET/CT scan performed and positive, rebiopsy before changing course of treatment.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Challenges of clinical trials in rare diseases

- Lack of preclinical models
- Difficulty generating interest from drug manufacturers
- Limited funding
- Limited number of centers with expertise
- Small patient population (more ideas than patients)
- FDA approvals can be challenging

Examples of ECD Studies

Phase II:

Long-term Outcome After Vemurafenib / BRAF Inhibitors Interruption in **Erdheim-chester Disease**

Dabrafenib and Trametinib in People With BRAF V600E Mutation Positive Lesions in **Erdheim Chester Disease**

Registry

Recruiting — Registry for Patients With **Erdheim-Chester Disease**

Quality of life

A Study of Memory, Thinking, and Brain Imaging in Adults With Histiocytosis

Conclusions

- Clinical trials are critical to improving treatments
- Participation in clinical trials can be intimidating but there are resources to help you
- We can learn from studies even when they don't involve new treatments
- There are barriers to conducting clinical trials in rare diseases but these can be overcome

- Learn more:
  - Clinicaltrials.gov
  - ECD Global Alliance