Clinical Trials – The New Frontier of Cancer Treatment

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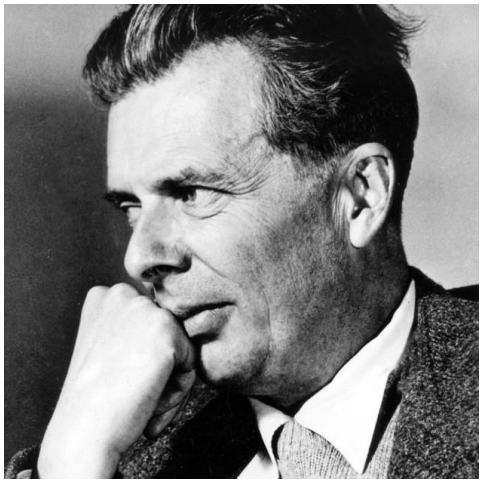
Saturday, April 11, 2015

The speaker has no financial or other conflicts of interest to disclose…

But I'll keep trying…

"The charm of history and its enigmatic lesson consist in the fact that from age to age, nothing changes and yet everything is completely different."



- Aldous Huxley

Discussion Topics

A Brief History of the Clinical Trial

Clinical Trials 101 – Key Concepts

Cancer Clinical Trials: Today's Landscape

New Clinical Trial Designs

A Brief History of the Clinical Trial

A Brief History of the Clinical Trial

Babylon – 562 BC

King Nebuchadnezzar

- Role of diet in human health
- Meat-rich v. legume-restricted
- First trial to guide a public health decision

Collier R. Legumes, lemons and streptomycin: A short history of the clinical trial. CMAJ : Canadian Medical Association Journal 2009;180(1):23-24. doi:10.1503/cmaj.081879.

A Brief History of the Clinical Trial

Persia – 1025 AD

Avicenna – Canon of Medicine

Set forth rules for drug testing:

- Drug must be pure
- Use for a "simple disease"
- Test on at least 2 types of disease
- Quality of drug related to strength of disease
- Timing of observations should rule out natural healing
- Drug effect must be reproducible
- Animal trials should precede human

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Bhatt A. Evolution of Clinical Research: A History Before and Beyond James Lind. Perspectives in Clinical Research 2010;1(1):6-10.

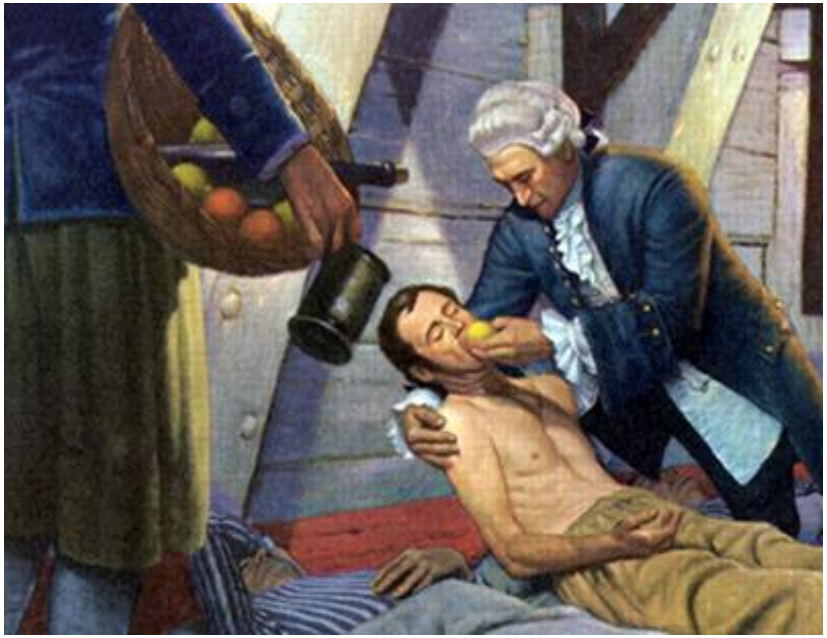
A Brief History of the Clinical Trial

Great Britain - 1747

James Lind – Father of the Clinical Trial

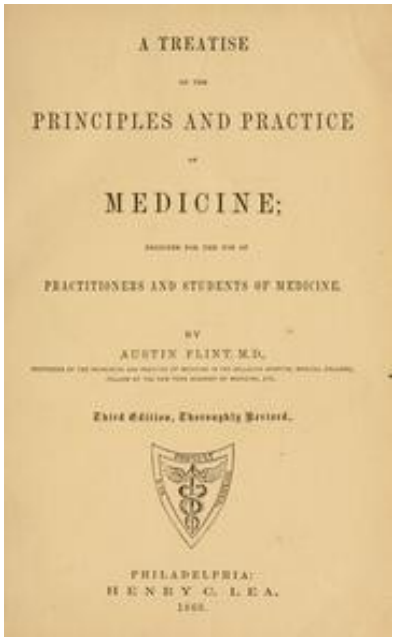
Treatise on Scurvy -1753

"They all in general had putrid gums, the spots and lassitude, with weakness of the knees."



- Isolation
- Groups of 2
- Six therapeutic interventions
- Documentation

A Brief History of the Clinical Trial


A TREATISE

ON THE

PRINCIPLES AND PRACTICE

OF

MEDICINE;

DESIGNED FOR THE USE OF

PRACTITIONERS AND STUDENTS OF MEDICINE.

BY

AUSTIN FLINT, M.D.,

Third Edition, Thoroughly Revised.

PHILADELPHIA:
HENRY C. LEA.

1863.

1863 – United States

Austin Flint – *A Treatise on the Principles & Practice of Medicine*

First utilization of a placebo

"The favorable progress of cases was such as to secure for the remedy generally the entire confidence of the patients."

A Brief History of the Clinical Trial

1946 – United Kingdom

Sir Austin Bradford Hill

Father of the Modern Clinical Trial

Streptomycin in Tubercolosis

- Meticulous trial design.
- Defined entry criteria and data collection.
- First widely publicized trial to incorporate *randomization*.

Clinical Trials 101 – Key Concepts

What is a Clinical Trial?

- Cancer clinical trials are research studies conducted by medical scientists to improve the care and treatment of cancer patients

- Cancer clinical trials test ways to:
  - Diagnose and treat cancer in people
  - Prevent or reduce disease or treatment side effects
  - Prevent a recurrence of cancer
  - Improve the comfort and quality of life of people with cancer
  - Understand non-medical factors that impact outcomes for cancer patients

Drug Development

Discovery of new drug in lab

Drug tested in lab and animals

- **Food and Drug Administration approves Investigational New Drug (IND) application**
- **The drug can now be tested in humans through a clinical trial**

Early Phase Clinical Trials

Phase 1 clinical trials

- What method of drug delivery and dosage is safest?
- How does the drug affect the human body?

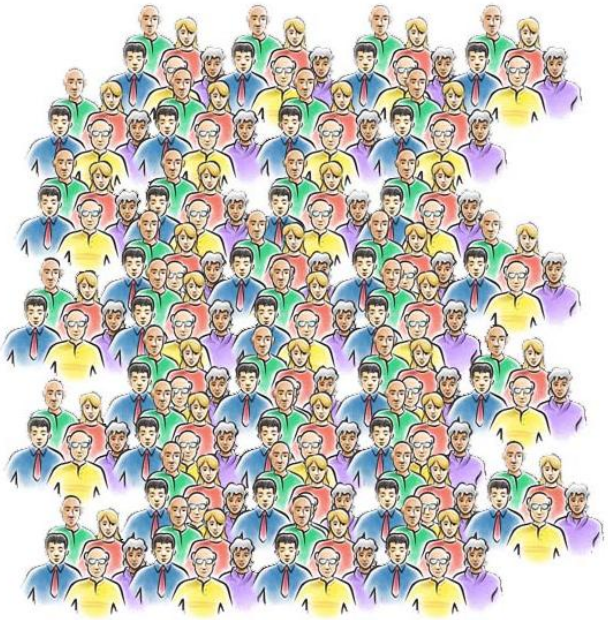
Phase 2 clinical trials

- Does the drug have an effect on the cancer?

Late Phase Clinical Trials

Phase 3 clinical trials

- Is the new drug or combination of drugs better than the best current treatment?



Researchers submit New Drug Application (NDA) to FDA

- FDA decides whether to approve the drug for use in all patients
- Is it more effective or does it have fewer side effects than standard treatment?

Continued Study

FDA approves new drug for sale and marketing in the United States

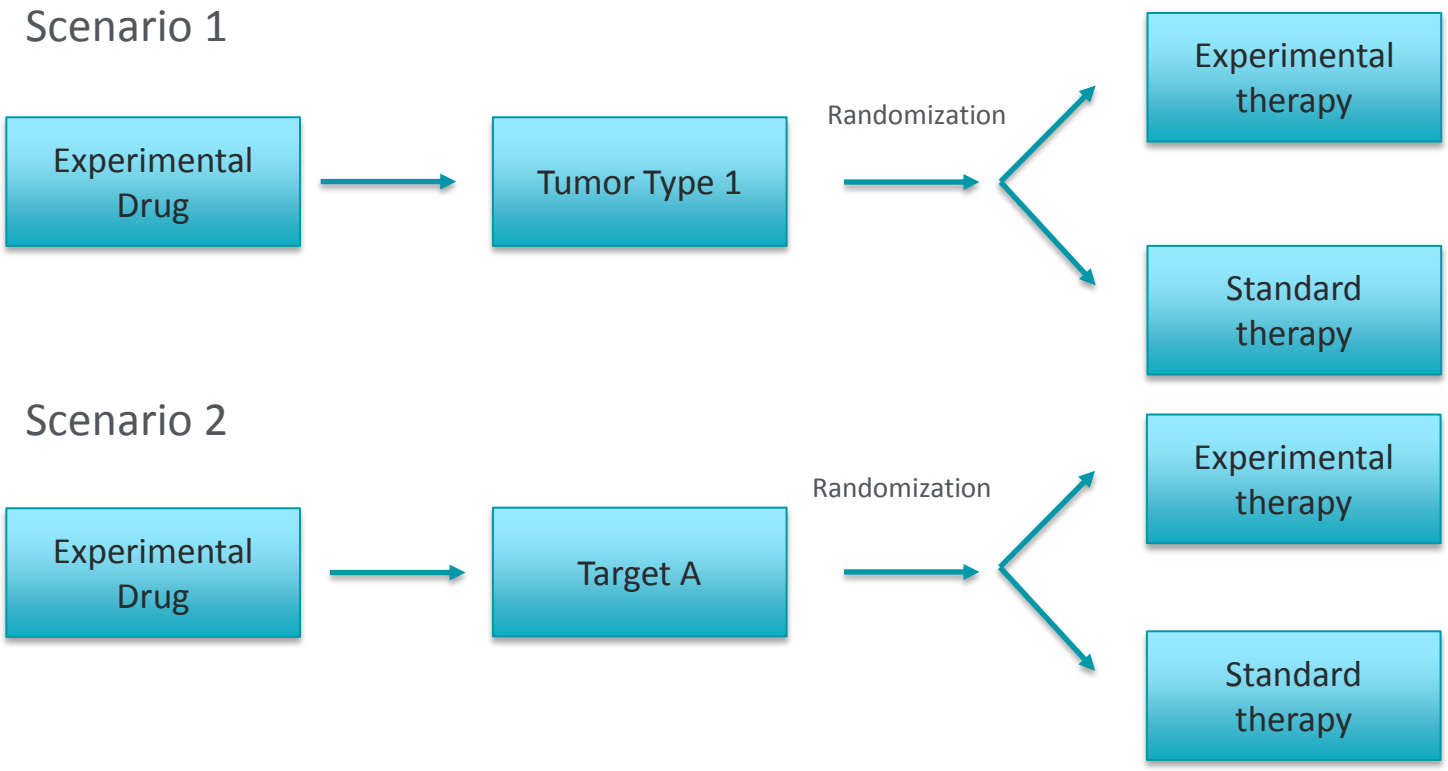
New drug available by prescription for all patients who need it

Phase 4 clinical trials

- Ongoing research
- Study the effectiveness or side effects of an FDA-approved drug over time in a large population of patients

Traditional Clinical Trial Design

One Tumor Type, One Experimental Therapy, One Standard Therapy



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Randomization

Randomization is the process of assigning clinical trial participants to treatment groups. Randomization gives each participant a known (usually equal) chance of being assigned to any of the groups. Successful randomization requires that group assignment cannot be predicted in advance.

Why Randomize?

If, at the end of a clinical trial, a difference in outcomes occurs between two treatment groups (say, intervention and control) possible explanations for this difference would include:

- the intervention exhibits a real effect;
- the outcome difference is solely due to chance;
- there is a systematic difference (or bias) between the groups due to factors other than the intervention.

Randomization aims to obviate the third possibility.

Clinical Trials: Myths and Misconceptions

If I enter a clinical trial, there's a good chance that I could receive a placebo

FALSE

Clinical Trials: Myths and Misconceptions

Clinical trials are the treatment of last resort

FALSE

Clinical Trials: Myths and Misconceptions

If I enter a clinical trial,
I'll be treated like a "guinea pig"

FALSE

Clinical Trials: Myths and Misconceptions

Care and treatment received are free

TRUE & FALSE

Clinical Trials 101: Summary

Before making any treatment decisions, ask questions and gather information.

The more information you have, the easier it will be to make decisions and manage challenges

Potential benefits of participation in clinical trials

- Receive, at minimum, the best treatment available
- Be among the first to benefit from a new treatment
- Receive a lot of attention and support, including close monitoring to ensure safety
- Have access to doctors with extensive experience in the type of cancer you have

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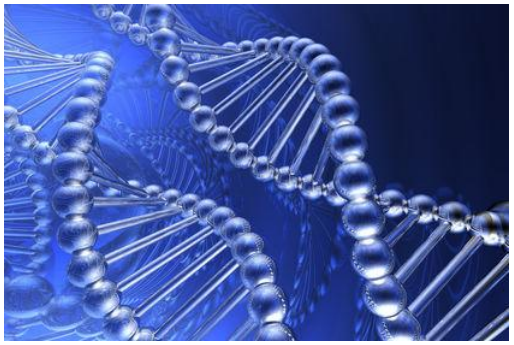
Cancer Clinical Trials: Today's Landscape

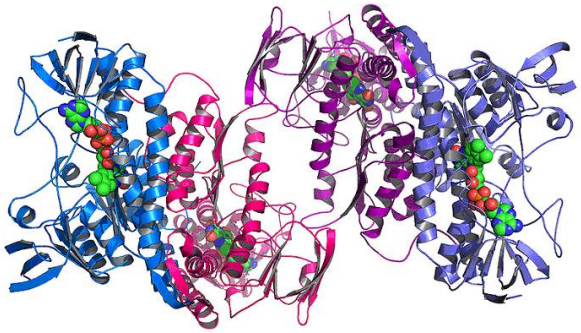
The Cancer Landscape in 2015

- 1.65 million new cases predicted
- Almost 600,000 cancer related deaths
- 5 year survival rate has improved from 49% in the 1970's to 68% from 2003-2009
- 14.5 million survivors compared with 3 million survivors in 1971
- Novel therapies becoming the norm – recent FDA approvals
    - Angiogenesis inhibitors – ramucirumab, sorafenib
    - Antibodies – obinutuzumab
    - Cell signaling inhibitors – dabrafenib, trametinib, idelalisib, ceritinib
    - Epigenome modifying agents - belinostat

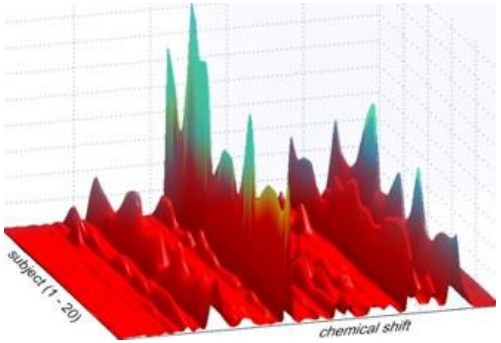
A Revolution in Cancer Therapy



Genomics



Proteomics



Metabolomics

Immuno-oncology

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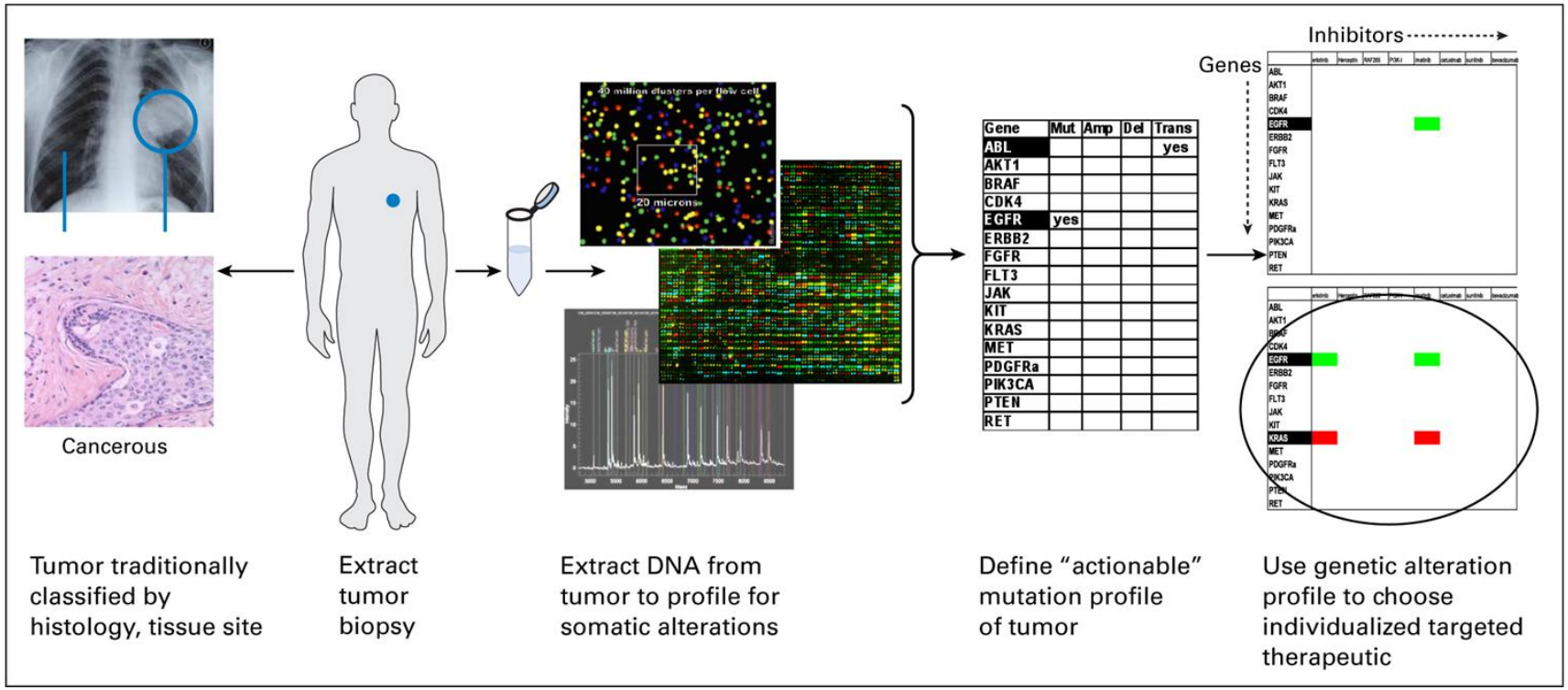
The Promise of Precision Medicine



MacConaill LE, Garraway LA. *J Clin Oncol* 2010;28:5219-5228.

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Problems with Current Trial Design

- Classical phase I,II, and III models require enormous resources
- Time to bring a new oncology drug to market 8-12 years
- Cost to bring a new drug to market can exceed $1 billion
- 70% of oncology drugs fail in phase II
- 59% of oncology drugs fail in phase III
- Have focused on histology-dependent strategies
- Limited collaboration between sponsors, academia, and funding sources
- Traditional models not designed to address “niche” agents with very small populations expected to benefit

Kaitin, KI, Dimasi JA. Pharmaceutical Innovation in the 21st century: new drug approvals in the first decade, 2000-2009. Clin Pharmacol Ther 2011; 89: 183-188.
KolaI, Landis J. Can the pharmaceutical industry reduce attrition rates? Nat Rev Drug Discov 2004 Aug; 3(8): 711-715.

Is There a Better Way?

Impact of biomarkers on clinical trial risk in breast cancer

Jayson L. Parker · Nadia Lushina · Prabjot S. Bal · Teresa Petrella · Rebecca Dent · Gilberto Lopes

Biomarkers and Receptor Targeted Therapies Reduce Clinical Trial Risk in Non–Small-Cell Lung Cancer

Adam Falconi, BSc, Pharm, Gilberto Lopes, MD, MBA,†‡ and Jayson L. Parker, PhD, MBA§*

In advanced breast cancer between 1998-2012:

- 14% of drugs in development were approved
- 23% of drugs in development approved when selecting for Her2 status
- Selecting for Her2 associated with a 27% reduction in costs

In advanced non-small cell lung cancer between 1998-2012:

- Biomarker targeted therapy was associated with a six-fold increase in trial success

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Parker, JL et al. Breast Cancer Res Treat. 2012 Nov;136(1):179-85.
Falconi, A. et al. Journal of Thoracic Oncology: Feb 2014 - Volume 9 (2): p 163–169

New Clinical Trial Designs

New Trial Designs

Methodologies

1. Biomarker guided design
    1. Basket trials
    2. Umbrella trials
2. Adaptive Design

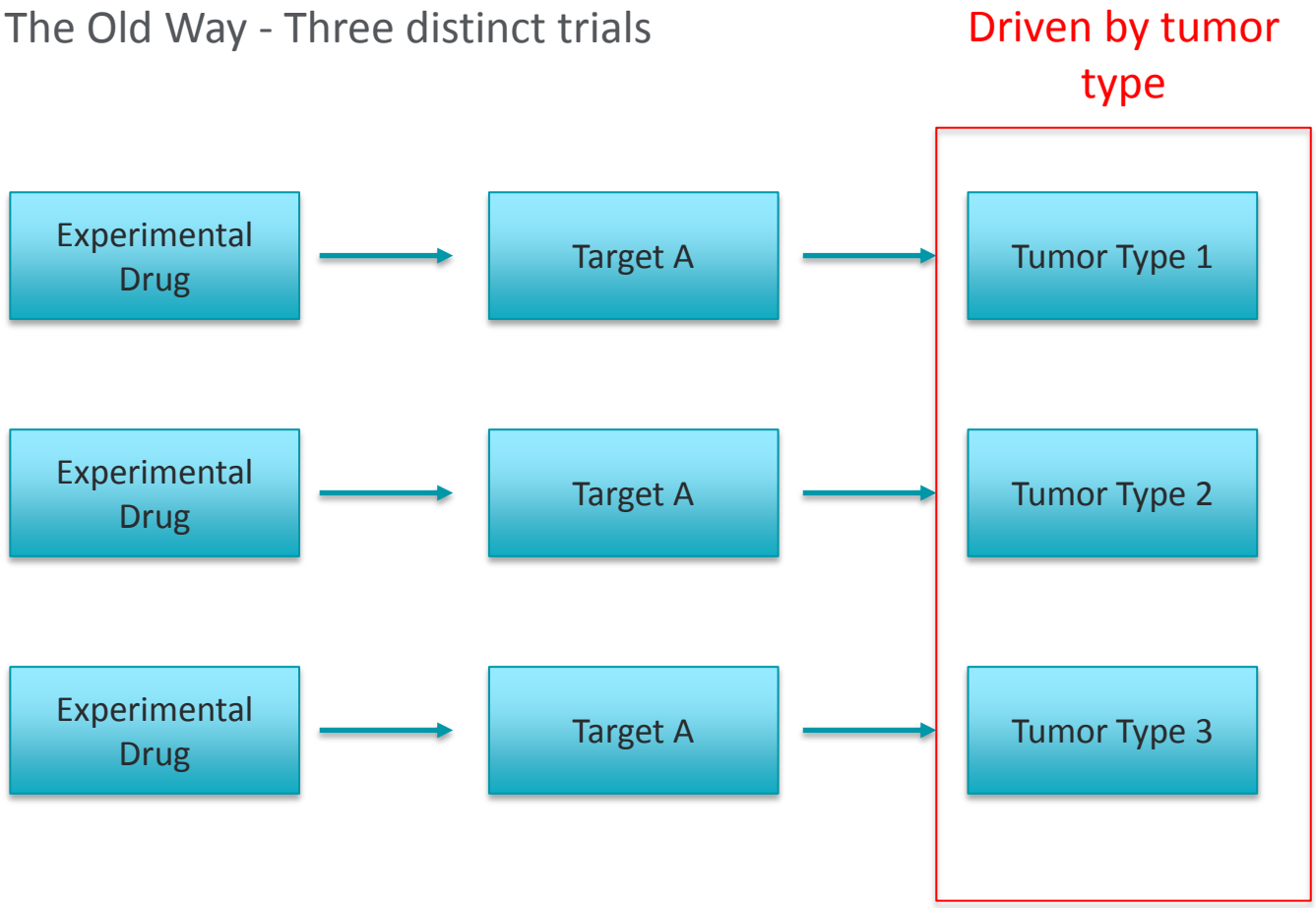
Major Goals

1. Shorten time to get drugs to the patients who need them
2. Reduce costs
3. Increase the number of trial participants getting the best treatment

Basket Trials

One Molecular Abnormality Targeted Across Multiple Tumor Types

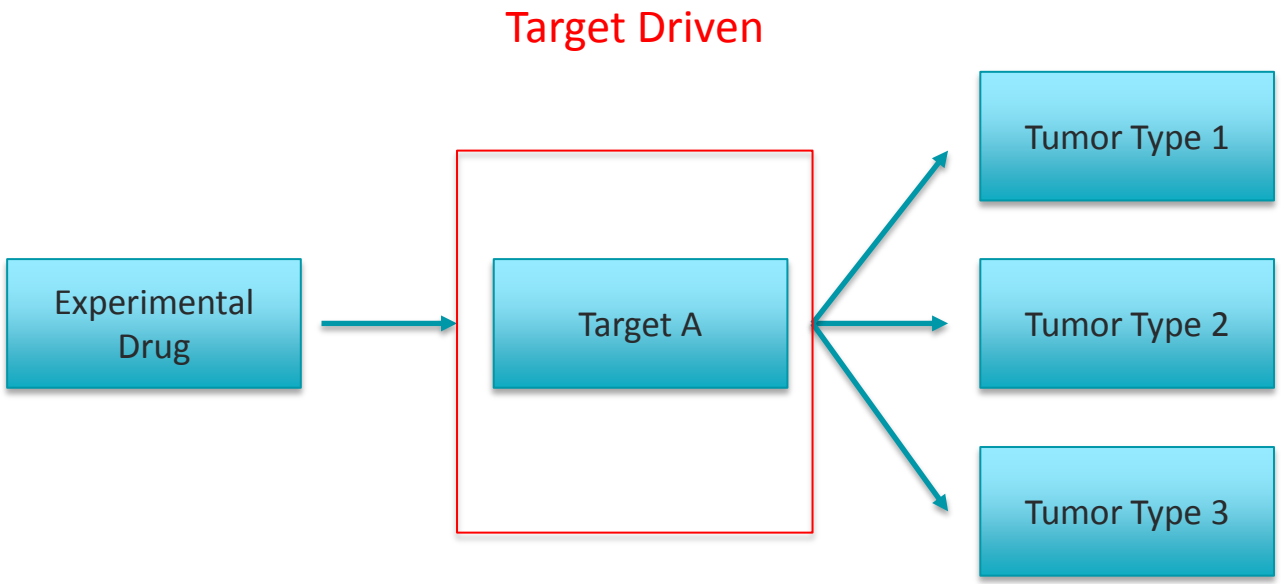
The Old Way - Three distinct trials



Basket Trials

One Molecular Abnormality Targeted Across Multiple Tumor Types

Simultaneous execution of multiple studies



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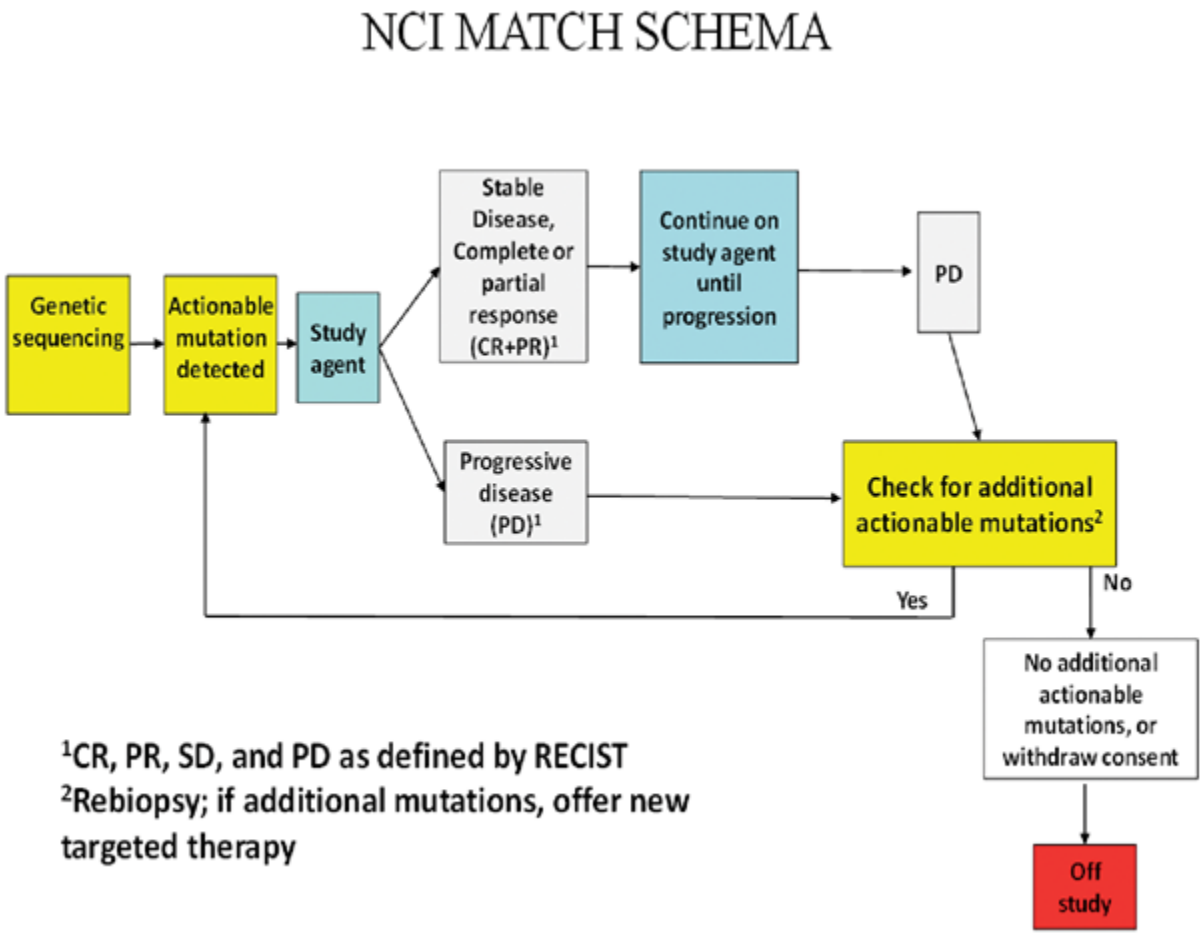
Redig, A. and Pasi, JA. Basket Trials and the Evolution of Clinical Trial Design in an Era of Genomic Medicine. Journal of Clinical Oncology, Vol. 33, 2015

NCI Molecular Analysis for Therapy Choice (NCI-MATCH)

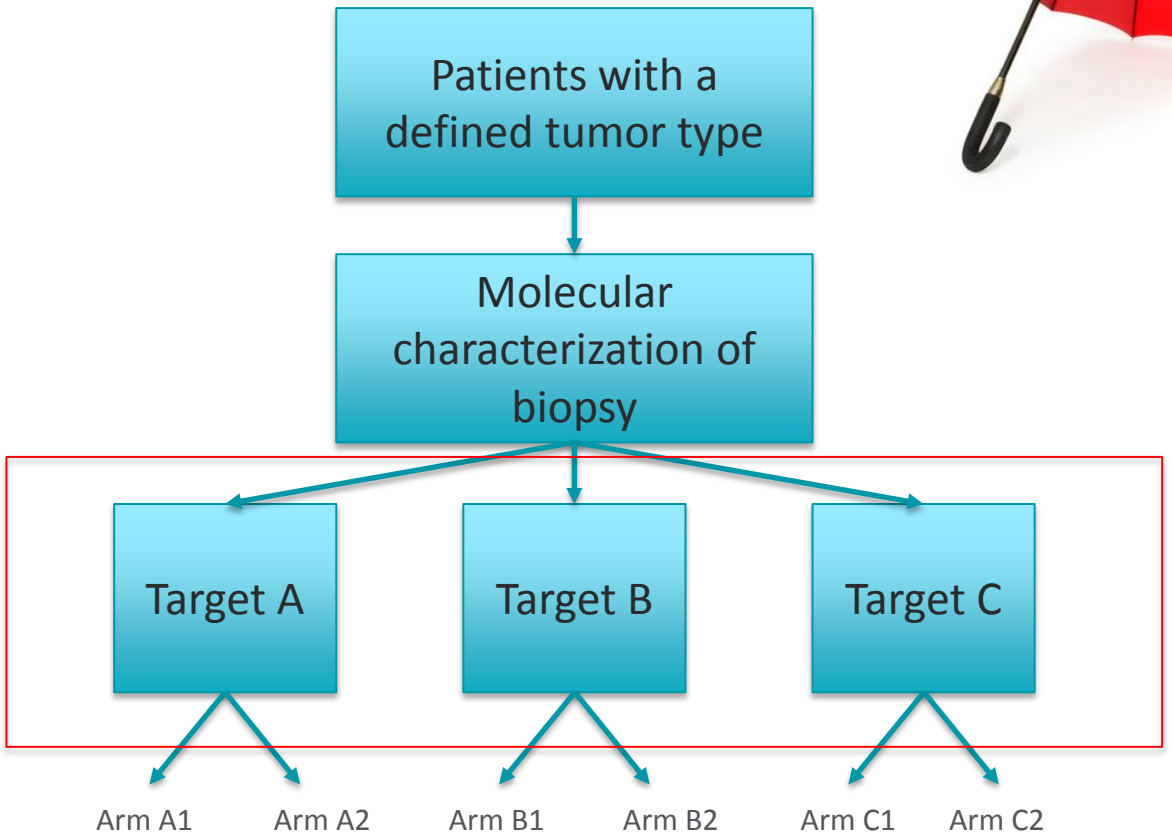


NCI-MATCH – Distinctive Features

- Discovery Trial – to inform anticipated larger phase II/III studies
- Over 40 drugs pledged
- More than 15 pharmaceutical companies participating
- More than 20 single arm, phase II studies conducted in parallel
- Arms can be added or deleted without impacting other arms

Umbrella Studies

One tumor type, multiple molecular targets



Histology
&
Target Driven

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Sleijfer, S et al. Designing Transformative Clinical Trials in the Cancer Genome Era. J Clin Oncol 31: 1834-1841.

Basket/Umbrella Trials Summary

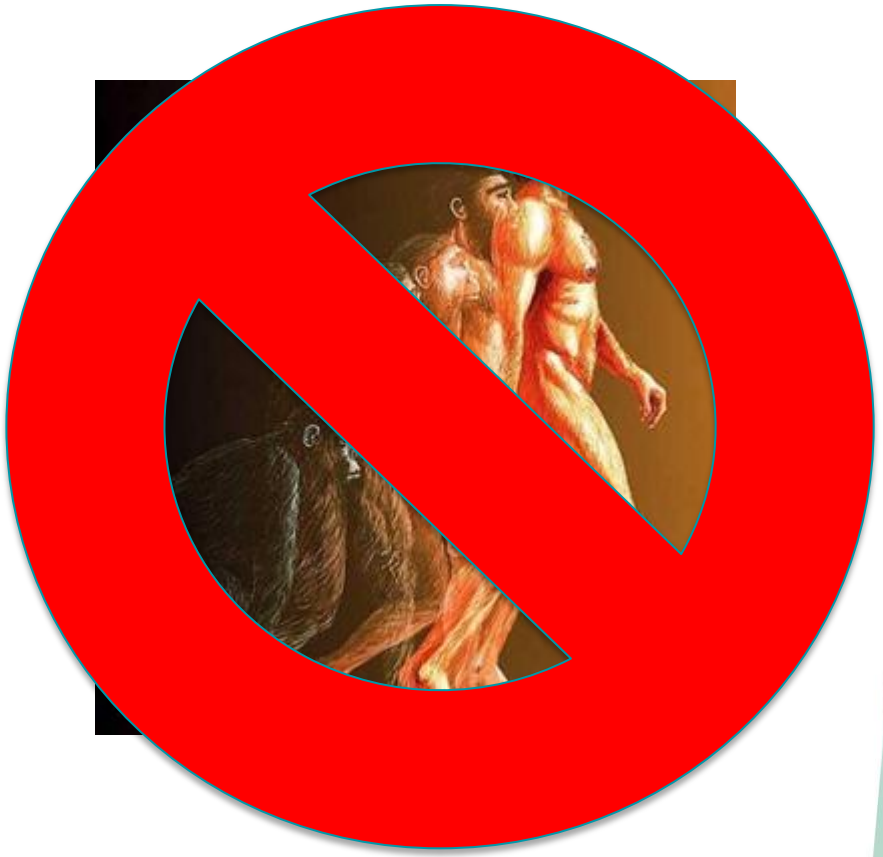
- A response to the explosion of potentially actionable mutations in human cancers.
- Resulting in an increase in public-private collaborations
- Promise efficiency in drug evaluation compared with traditional histology-driven sequential studies
- Appear optimally positioned to evaluate large effects of targeted agents on relatively rare targets
- Can detect strong hints of activity in early phase studies if appropriately designed
- Suggest of different types with shared molecular aberrations may be more similar than tumors from same type lacking molecular features
- Most established in the Phase II setting with increasing exploration in Phase III

Adaptive Trial Designs

Adaptive Trial Designs

Key Features

Planned modifications based on accumulating data within a study that does not undermine the validity or integrity of the study.



Trial Procedures:

Eligibility	Study Dose
Endpoints	Treatment Duration
Response Evaluation	Diagnostic Procedures

Statistical Procedures:

Randomization	Sample size
Data Monitoring	Statistical Analysis Plan

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Chow, SC and Chang, M. Adaptive design methods in clinical trials – a review. Orphanet Journal of Rare Diseases 2008, 3:11

Adaptive Trial Designs

Key Features

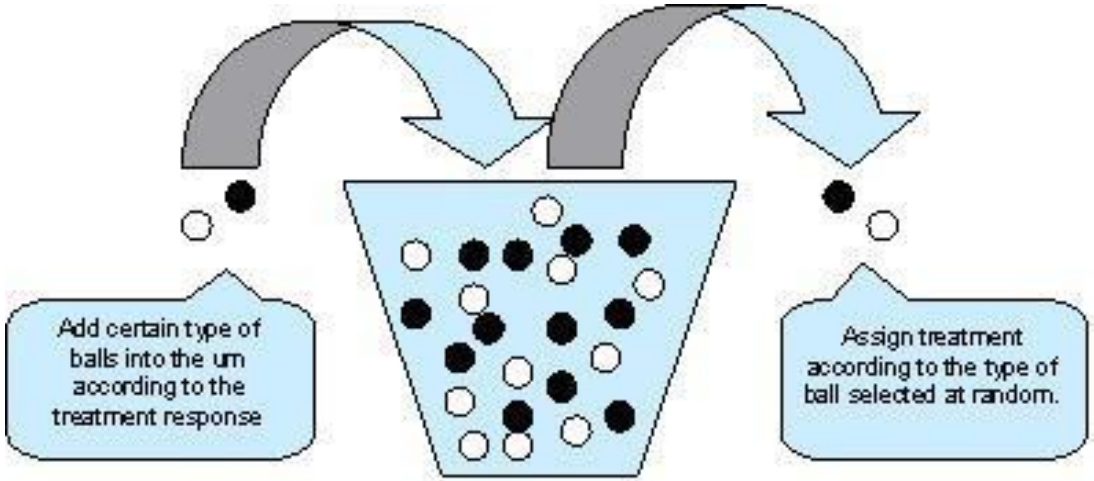
1. All changes are pre-planned
2. Allows the trial to “learn” from early results
3. Can increase the proportion of patients getting the better treatment
4. May shorten the time it takes to complete the trial
5. Can be very complex to manage

Adaptive Trial Designs

Adaptive Randomization

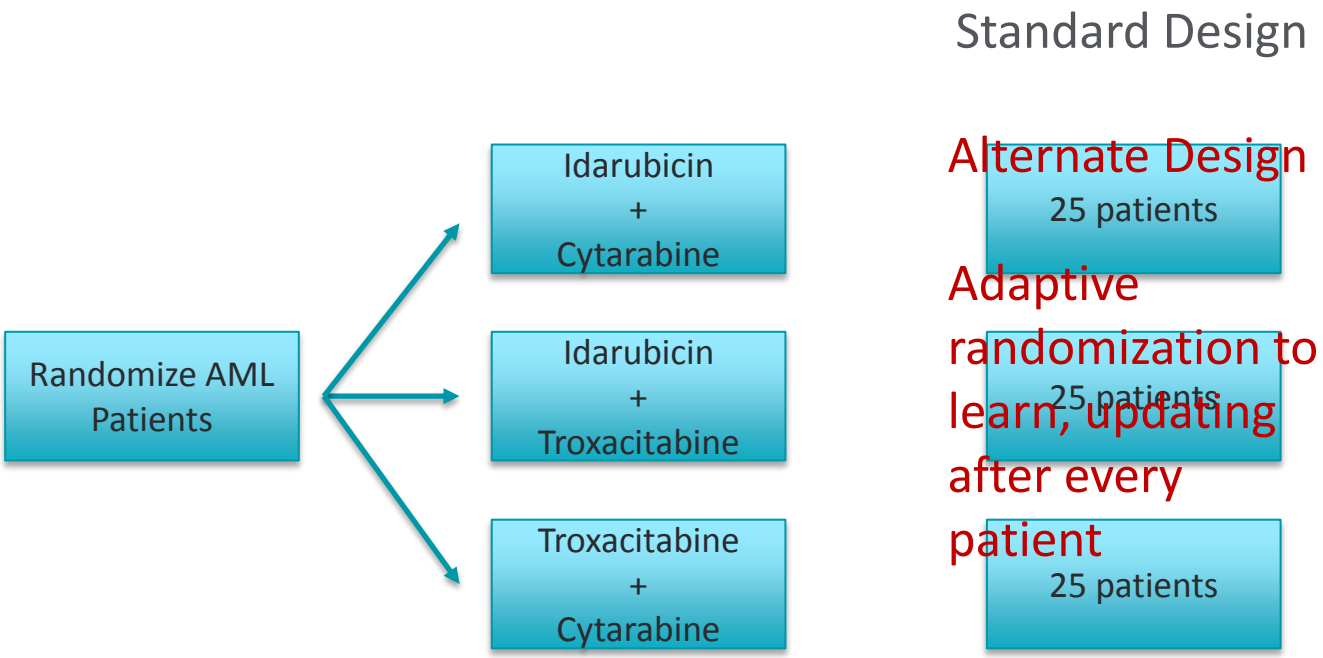
Adaptive Trial Designs

Adaptive Randomization



Adaptive Trial Designs in Action

Troxacitabine in Acute Myelogenous Leukemia



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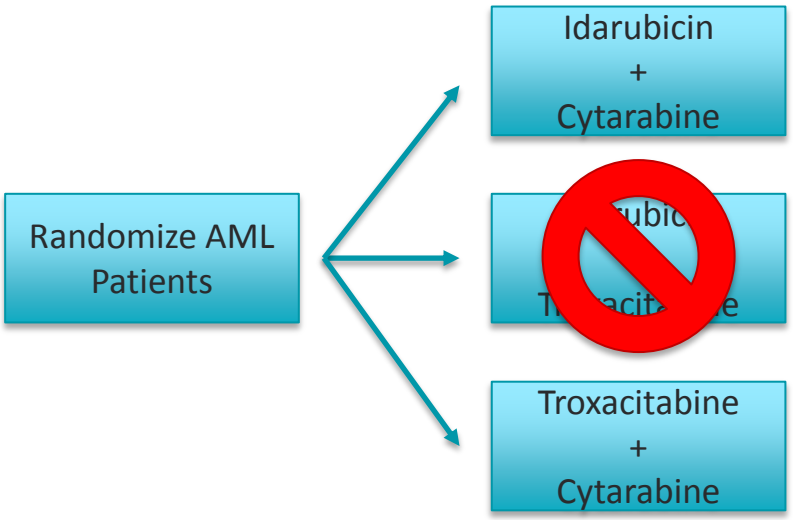
Giles et al. Journal of Clinical Oncology, 2003.

Adaptive Trial Designs in Action

Assign with higher probability to the better performing treatment



This arm dropped after 24th patient

Trial stopped after 34 patients

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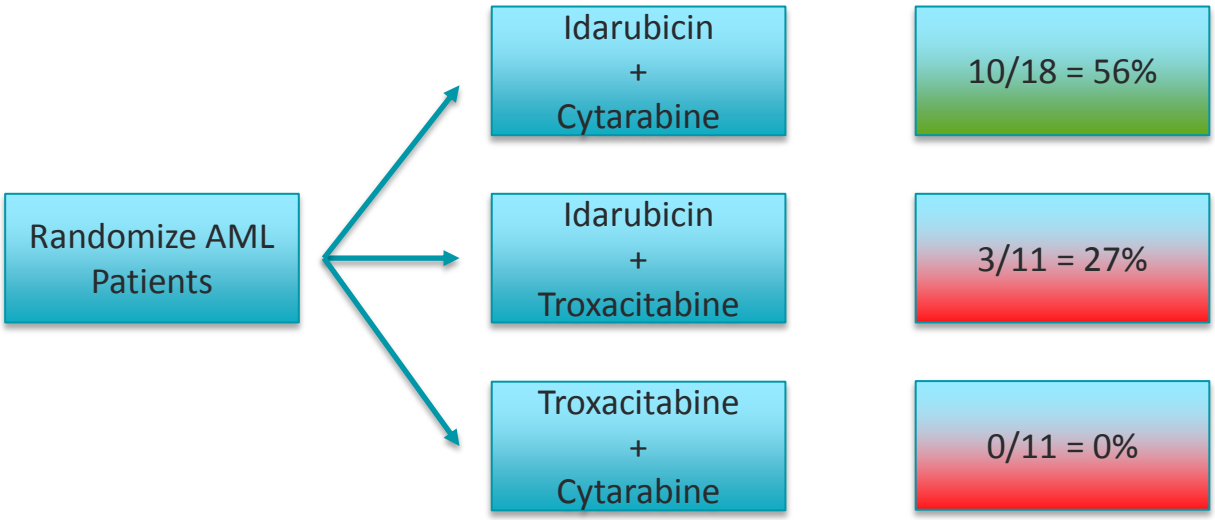
Giles et al. Journal of Clinical Oncology, 2003.

Adaptive Trials in Action

Summary of Results – Complete Response by Day 50



Strengths of Bayesian Adaptive Trials

- Potentially smaller trials
- Potentially shorter trials
- More accurate conclusions
- Able to address more questions
- Better treatment for patients in clinical trials
- Greatest potential in multi-armed trials
- Benefits limited but real in two-armed trials
- Suited to the task of pairing molecular signatures to targeted agents

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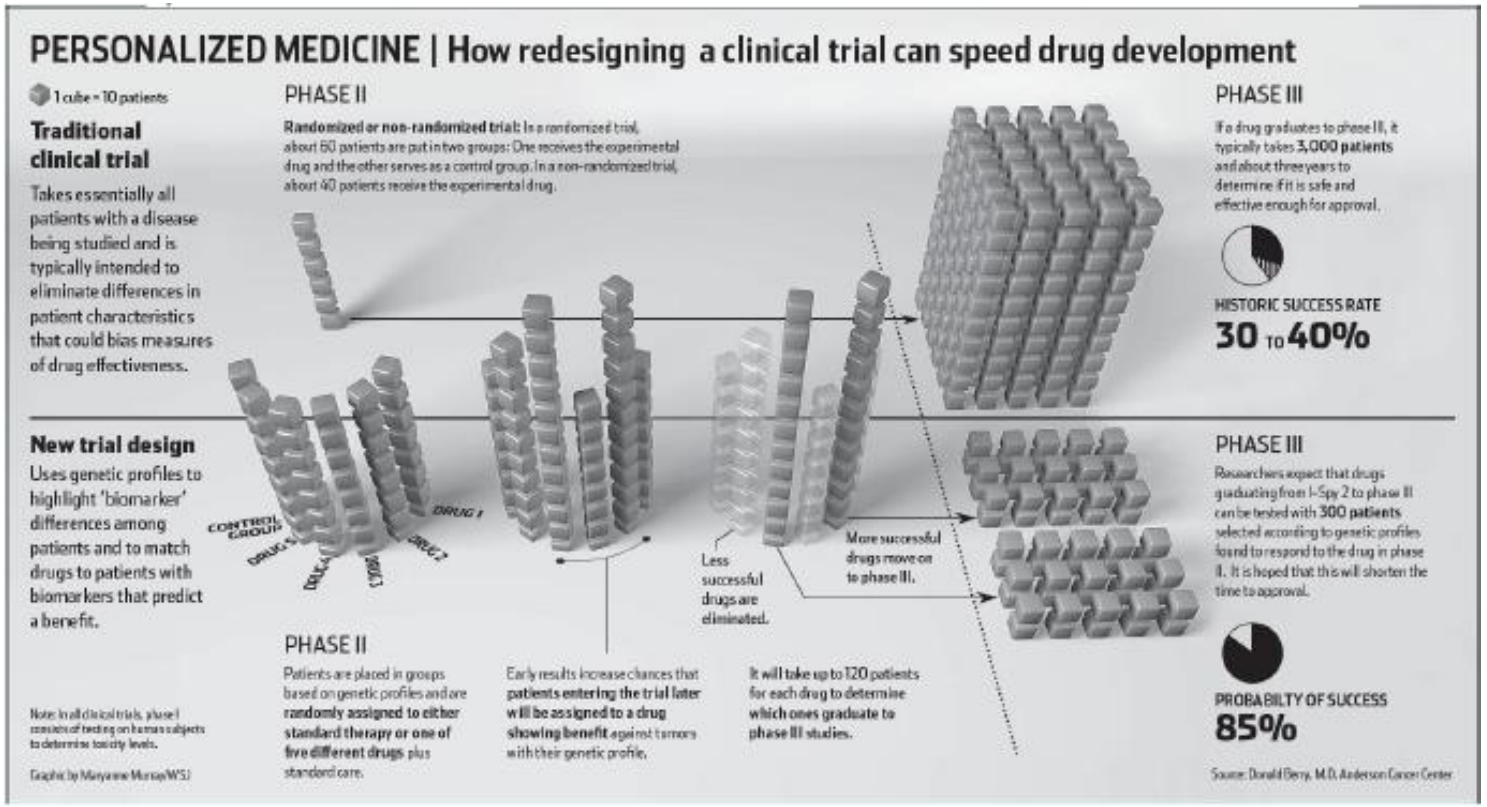
Berry, DA. Adaptive Clinical Trials: The Promise and the Caution. J Clin Oncol 29: 606-609.

The Promise of New Trial Design

Too good to be true?



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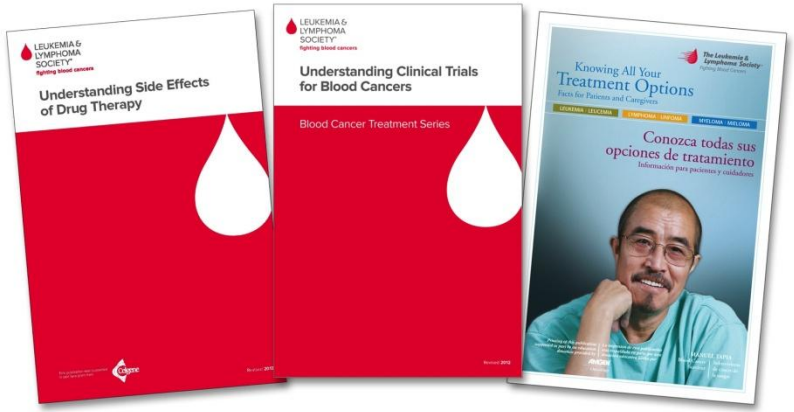
Thank you.

Where to learn more

- If your doctor does not bring up clinical trials as a treatment option, don't hesitate to ask
- Speak with an LLS Information Specialist
- Use the free LLS-supported TrialCheck®, powered by eviti® | Clinical Trials to find clinical trials near you through the LLS website www.LLS.org/clinicaltrials
- Refer to LLS booklets and listen to telephone/web education programs on your diagnosis and emerging therapies



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- www.LLS.org/clinicaltrials, **click on** 

- **TrialCheck® search tool***
  - Assists user to identify clinical trials that meet eligibility criteria for a specific patient
  - Asks 11 simple questions about the patient
    - Questions include zip code, disease diagnosis and stage, treatment history and the patient's age
    - Most questions are optional, but providing information allows TrialCheck to eliminate trials for which the patient is not eligible
  - Once the search is complete, clinical trials are organized by location, showing those closest to the patient first
  - Allows you to save your search results
  - Allows you to sign up to receive updates when a new trial has been added to your search results
  - LLS Information Specialists can help
    - (800) 955-4572

**TrialCheck® powered by eviti® | Clinical Trials*

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- Past telephone/web education programs www.LLS.org/pastprograms
- Webcasts www.LLS.org/webcasts
- TrialCheck www.LLS.org/clinicaltrials
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