Genome-Forward Trials and Design Challenges

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• LISA, YOU ARE THE BEST

• An anonymous fan
Breast cancer treatment is informed by old-fashioned trials that were: large, rigorous, and provided level I evidence. In light of modern technology how do we transform further?

Challenges to meaningful clinical trials in the 'omic era:
1. “Breast cancer” doesn’t exist, is now a fragmented group of biologically distinct entities.
2. Patients have much better outcome across the spectrum of disease (good for them, bad for event rates)

How will we develop drugs and treatment approaches if cancer is a group of orphan diseases?
Historical Transformative Trials

ATAC (HR+)

CALGB9741 (any)

HERA (HER2+)

Large, rigorous, clearly defined
Often modest effects

Nearly impossible now...
Too big
Too unselected
Too many competing good ideas

\(N \sim 3200\)

\(N \sim 2000\)

\(N \sim 3400\)

(of \sim 10k in adjuvant trials)

Cuzick, Lancet Oncol 2010; Gianni Lancet Oncol 2011; Citron, JCO 2003
Breast Cancer Heterogeneity: Multiple Distinct Subtypes

- ER+ subtypes
- ER- subtypes
- Claudin-low subtypes
- Basal-like subtypes
- HER2-enriched subtypes
The Cancer Genome Atlas Project: Basal-like Breast Cancer

- **22% Amplified, 0 mutants**
- **32% Amplified, 1 G12V mutant**
- **31% Amplified, 1 mutant (not V600E)**
- **50% High expression, Moyano et al., 2006**

**MEK1-pathway**
- **total = 80% with some possible pathway activating event**

**PIK3CA-pathway**
- **total = 89% with some possible pathway activating event**

**Cluster 1**
- **Cluster 2**
- **Cluster 3**

Courtesy Chuck Perou
Basic tenets of clinical research:

- Test a defined hypothesis
- Minimize the risk of incorrect answers
  - Type I error – saying something is different when it isn’t
  - Type II error – saying something isn’t different when it is
Trials in the 21st Century

- Small
- Fast (collaboration is key)
- Rational
- Careful!
  (esp marker development, trial design)
“Genome-Forward” Trials

• Pro:
  – Biologically rational
  – Increasingly feasible
  – Enriched population – can set success threshold high
    • Crizotinib-like?

• Con:
  – Screening burden
  – Expense
  – Target challenges
    • Is this really a driver?
    • Is the assay valid?
    • Does the drug hit the target?

This is not a new paradigm
Predicting Targetability is Not Easy

PI3K Pathway activating mutations vs phosphoproteins vs signature

TCGA, Nature 2012
Abstract

**Purpose** Surgical resection plus adjuvant platinum-based chemotherapy is considered standard care for stage II to III non–small-cell lung cancer (NSCLC), but its efficacy is limited, and it involves toxic risks, justifying patient-tailored treatment. Excision repair cross-complementation group 1 (ERCC1) is known to predict cisplatin-based chemotherapy response; EGFR mutations were predictive of epidermal growth factor receptor inhibition response.

**Patients and Methods** This prospective randomized phase II trial enrolled 150 patients with completely resected non–squamous cell stage II or IIIA (non-N2) tumors. Patients in the control arm (n = 74) were treated with four standard-dose courses of cisplatin plus pemetrexed (CP). In the customized treatment arm (n = 76), patients with activated EGFR mutations received erlotinib 150 mg daily for 1 year; ERCC1-negative patients received four CP courses, whereas ERCC1-positive patients underwent follow-up. The trial sought to demonstrate the feasibility of customized adjuvant chemotherapy, based on timely biomarker analysis within a 2-month postsurgery delay. Secondary objectives were tolerability, compliance with adjuvant therapy, and biomarker distribution.

**Results** In arm A, all patients received CP; in arm B, seven received erlotinib, 53 were administered CP, and 16 underwent follow-up. Median erlotinib exposure was 344 days. Of the 127 patients allocated to CP, 82% received four cycles with good tolerability. The overall success rate of the trial (ie, percentage of patients with complete biomarker status who were able to start adjuvant treatment within 2 months of surgery) was 80%.

**Conclusion** The primary end point of the trial was met, demonstrating the feasibility of a national biology-driven trial in the adjuvant NSCLC setting. Nevertheless, the phase III part was canceled because of the unreliability of the ERCC1 immunohistochemical readouts.
pCR by Intrinsic Subtype in HER2+
C40601 all arms (trastuzumab, lapatinib, both)

Even with “driver” abnormalities and known drugs, other factors affect response

Carey et al, ASCO 2013
Trial Designs Popular Now

- Umbrella (assign defined cancer type by molecular aberration)
- Basket (assign by molecular aberration regardless of tumor type)
- Neoadjuvant (smaller, faster, allow tissue studies)
- Window (study biology and resistance)
- Adaptive (can be used with several designs, smaller, nimble)
Umbrella Trials
e.g. SAFIR01, AURORA

Genotype all patients of a particular disease

Allocate patients to particular drugs based upon profiling results

- EGFR inhibitor
- BRAF inhibitor
- MEK inhibitor
- AKT inhibitor
- mTORC1 inhibitor
- Chemo

Series of phase II studies

Pro 😊:
- Appealing
- Rational

Con 😞:
- Often depends on unproven drug
- Often depends on unproven assays
- Endpoints more difficult (not PFS, OS)
Example: Neratinib for HER2 Mutation-Positive Breast Cancer

Activating mutations in HER2
Sensitive to neratinib
~ 5% of HER2-negative tumors

Bose R et al, Cancer Discovery 2013

HER2 gene amplification negative Stage IV Breast Cancer

Tumor DNA Sequencing for HER2 Mutation

Mutation Absent

Mutation Present

ineligible

Neratinib 240 mg po qd

Very strong rationale for single agent approach.
However: ~125 screened / trial pt. Poor efficiency unless part of umbrella genotyping effort. Will affect very small %.
Basket Studies
e.g. NCI-MATCH, Novartis Signature Trials

- Colorectal Cancer
- Lung Cancer
- Breast Cancer
- Ovarian Cancer
- GBM
- Etc...

Pro:
- Appealing
- Rational

Con:
- Lineage specificity
- Biomarker reliability/accuracy
- Same endpoint problems
“Window of Opportunity” Trials

- **Pro 😊:**
  - Proof of principle
  - Biomarker discovery

- **Con ☹:**
  - Can’t use really new agents (safety issues)
  - Hard to test combinations (dose?, toxicity issues)
  - No clinical data

*These contribute to scientific knowledge and therapeutic hypotheses, not clinical care*
Neoadjuvant Trials

**Pro ☺:**
- Pick-a-winner
- pCR is a good surrogate endpoint (FDA registrational option)
- DFS/OS can be collected in same cohort (underpowered)

**Con ☹:**
- pCR only validated endpoint. Irrelevant in many (ER+)
- Quantitative relationship pCR to DFS/OS not established
- Macromet = micromet?
- Drugs must be well known

*Can contribute to clinical care, excellent way to get clinical + biologic information*
Neoadjuvant Chemotherapy Challenges

pCR predicts DFS and OS

**True**

...Ergo

pCR \( \uparrow \) = DFS and OS \( \uparrow \)

*Not so fast...*

The only trial with significant impact on outcome was NOAH (which tested trastuzumab versus not)

Cortazar et al, Lancet 2014

\( \bigcirc \) = significant \( \Delta \) pCR
Residual Disease Trials

New Diagnosis

- Pro 😊:
  - Tissue available
  - Resistant tumors
  - High risk population

- Con 😞:
  - Adjuvant-size trial
  - Cannot assess response (event = relapse), needs to be randomized
Adaptive Trials

- **Pro 😊:**
  - Pick-a-winner
  - Can adapt on drug or biomarker
  - Conserve resources
  - Faster. Smaller (?)

- **Con 😞:**
  - Reliability of interim estimates?
  - Higher error risk
  - Complicated
  - If biomarker works – lose discovery options
Where Are We Going?

• Precision medicine is coming...but how precise?

• There are real challenges to trial design in the genomic era – power, effect size, adequate diagnostic assays

• We will need to rely on smaller, less stringent clinical trials and pharmacodynamic studies.

• We are up to the challenge!
Thanks

THE END
What Do We Mean By Genome-Forward?

- Trial design incorporates genetic/genomic data.
  - Could include proteomic/metabolomic/etc… Design issues would not change.
- Overlapping concept with “precision medicine”, “personalized medicine”, “individualized medicine”
Implications of Adaptive Trials

Adaptive Design (Biomarker Guided) (n=150-200)
- Integral biomarker (M) (must be validated)
- Smaller if M+ works
- Expensive and complex (need M real-time)
- Can’t test other promising markers now or later

Randomized Design (n=400-500)
- Integrated biomarkers (should be validated)
- Larger
- Expensive overall but less complex
- Can test more markers prospectively or prospec/retro

2nd assessment of Objective Response Rate, or Progressive Free Survival

BIOMARKER 1
PIK3CA mutation

BIOMARKER 2
LumA vs LumB

BIOMARKER 3
PTEN loss (IHC)

BIOMARKER 4
AKT1 mutation

BIOMARKER 5
pAKT (IHC)

BIOMARKER 6
Expression Signature(s)

BIOMARKER 7
others

Progressive Free Survival
BY BIOMARKER
Cancer Evolution

Myeloma clonal dynamics (aCGH) with therapy

Initial disease

Current disease

One patient’s breast cancers (sequencing)

Is this where CTC, free DNA, etc will help us?

Keats. Blood 2012

Unpublished data
Adaptive Response to Therapy May be Predictable

Acquired ESR1 mutations post endocrine Rx

Ligand-binding domain mutations are frequent in aromatase inhibitor-resistant breast cancer

Metastatic samples (22%):
- 6 of 11 (55%) by Robinson et al, 2013
- 9 of 36 (25%) by Toy et al, 2013
- 5 of 41 (11%) in BOLERO Trial, 2013

Primary Samples (<1%):
- 6 of 183 (3%) in BOLERO Trial
- 0 of 46 (0%) by Ellis et al., 2012
- 0 of >500 (0%) in TCGA

Reprogramming in response to kinase inhibitors

MEK inhibition erodes

As other kinases are induced

Jeselsohn, SABCS 2013 (CCR in press); Duncan et al, Cell 2012
Modern Challenges

• Lots of genetic aberrations
  – Hundreds across the breast cancer spectrum – what is important?
  – Many affect small populations E.g. HER2 activating mutations, AR

• Uncertainty about identifying targetability
  – Gene / RNA / protein?

• Explosion of biologically-directed agents
  – Single agent?
  – Combinations?
  – Circumventing resistance?

• Tumor evolution and tumor microenvironment
How long if only relevant for 2% of breast cancers?