Endpoints and Novel Designs in the Era of Targeted Therapies

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Endpoint Hierarchy

- True clinical efficacy measure
- Validated surrogate endpoint *(Rare)*
- Surrogate endpoint “reasonably likely to predict clinical benefit”
- None of the above: A correlate that is solely a measure of biological activity
Endpoints: Fit to purpose

- Phase II goal: Go/No-go phase III decision
  - Historically: Endpoint with good correlation with clinical benefit outcomes ok
  - Reconsidered: If goal is successful phase III trial, more rigor in phase II endpoint is appropriate
- Phase III goal: Agent approval
  - Clinical benefit or validated surrogate endpoint needed
Phase II endpoints

- Tumor response (RECIST)
  - Patients live longer even without response\(^1\)

- Novel imaging
  - Cannot validate a new endpoint and a new therapy in the same trial

- PFS at an early time point
  - Captures disease stabilization

\(^1\)Grothey JCO 2008
Patients without response benefit from better therapy

IFL +/- Bev

FOLFOX vs 5FU/LV

Grothey, JCO 2008
Phase III Endpoints: FDA Regulatory Standard

- Safe and Effective
- Effective (clinical benefit)
  - Live longer
  - Live better
- Live better very difficult to show in oncology
Surrogate validation: Requires meta-analysis

May 05, 2004: ODAC recommends 3-yr DFS as new regulatory endpoint for FULL approval in adjuvant colon cancer

\[ r = 0.90 \]

5 yr OS = 0.0002 + 0.998 * 3 yr DFS

18 Trials, 20,000+ patients

Sargent et al., JCO 2005
Is PFS a Clinical Benefit Endpoint?  
Opinion: Pro

- "I have no problem accepting that, in a lethal disease such as metastatic cancer, delaying progression is a clinical benefit in itself, provided that the magnitude of the benefit is sufficient and the side-effect profile acceptable."

Merits of PFS as an endpoint

• Un-encumbered by cross-over
• Available more quickly than OS
• Variable demonstration of surrogacy for OS
  • Colon (before biologics)– Yes – Buyse JCO 2007
  • Breast – No – Burzykowski, JCO 2008
  • Lung – Unclear – Buyse ASCO 2008
PFS vs. OS in modern First line colon cancer trials

• ARCAD database: Individual patient data from 22 First line trials, 1997-2006
  - 16,762 patients
  - 12/22 tested targeted therapies

Shi et al, JCO 2014 to appear
Trial level treatment effects:
PFS vs. OS

\[ R^2 = 0.54 \]

Shi et al, JCO 2014
To appear
Post-progression challenges

- Out of protocol’s control
  - Perhaps unbalanced
  - Some crossovers without prog

- Same benefit in $\Delta$PFS, even if directly translates to $\Delta$OS, results in smaller HR
  - PFS: 6 mo v 9 mo: $HR=0.66$
  - OS: 12 mo vs 15 mo: $HR=0.80$
    - 15 mo vs 18 mo: $HR=0.83$
    - 21 mo vs 24 mo: $HR=0.875$

- Implication: PFS trials inherently underpowered for OS
Power for OS with 2-month PFS & OS Advantage

Probability of statistical significance in OS

Median OS (months) after progression

Broglio, JNCI 2009
Impact of Post-Progression survival on surrogacy

SPP=Survival Post-Progression

Broglio, JNCI 2009
Impact of Post-Progression survival on Surrogacy

SPP=Survival Post-Progression

Broglio, JNCI
2009
PFS as a surrogate endpoint

• Is PFS a surrogate for OS in cancer?
  • When no effective 2nd line rx: Yes
  • When effective 2nd and later lines rx: likely no

• As survival beyond progression lengthens, surrogacy becomes difficult
  • Attenuated HR
  • Additional noise

• Only currently realistic endpoint for phase III trials in diseases with multiple lines of therapy
Biomarkers: Predictive Marker

Single trait or signature of traits that separates different populations with respect to the outcome of interest in response to a particular (targeted) treatment
Enrichment Design

- Screens patients for the presence or absence of a marker or a panel of markers, AND
- Only includes patients in the clinical trial who either have or do not have a certain marker characteristic or profile

Paradigm: Not all patients will benefit from the study treatment under consideration
- Understand the safety, tolerability and clinical benefit of a treatment in the subgroup of the patient population defined by a specific marker status
Enrichment Designs

Appropriate when:

• Mechanism of drug action is known
• Assay is reliable
• Compelling preliminary evidence suggesting that patients with or without that marker profile do not benefit from the treatments in question
• Needs fewer overall randomized patients compared to an “untargeted” design
Trials in targeted populations

• Gains in efficiency depend on marker prevalence and relative efficacy in marker + and marker - patients

(Simon & Maitournam, CCR 2004)
ToGA trial design

Phase III, randomized, open-label, international, multicenter study

3807 patients screened
810 HER2-positive (22.1%)

HER2-positive advanced GC (n=584)

5-FU or capecitabine + cisplatin (n=290)

5-FU or capecitabine + cisplatin + trastuzumab (n=294)

Stratification factors
- advanced vs metastatic
- GC vs GEJ
- measurable vs non-measurable
- ECOG PS 0-1 vs 2
- capecitabine vs 5-FU

Chosen at investigator’s discretion

Bang et al; Lancet 2010

GEJ, gastroesophageal junction
TOGA Primary end point: OS

Bang et al; Lancet 2010
Unselected Designs

- **Sequential Testing Strategy Designs**

- **Marker based strategy design**
  - Randomize subjects to treatment either based on or independent of the marker status

- **Marker by treatment interaction design**
  - Use the marker status as a stratification factor when randomizing subjects to treatment

All patients of a specific disease type and stage are eligible for the clinical trial, regardless of their actual marker status.
Sequential testing: MaST Design

- Test marker positive first at $\alpha_1 (< 0.025)$
- If positive, test marker negative at full $\alpha (0.025)$
- If not positive, test overall treatment effect at level $\alpha - \alpha_1$

Friedlin, Clin Trial 2013
Unselected Design: Upfront Stratification by Marker status

Register → Test Marker → Marker Level (-) → Randomize → Treatment A

Marker Level (+) → Randomize → Treatment B

Power trial separately within marker groups

Sargent et al., JCO 2005
Unselected Design: Marker Based Strategy

Register

Randomize

Test Marker

Marker Based Strategy

Marker Level (-) → Treatment A

Marker Level (+) → Treatment B

Non Marker Based Strategy

Randomize

Treatment A

Treatment B

Sargent et al., JCO 2005
Beyond one mutation at a time: Umbrella Trials

- Better treatment of cancer by choosing therapies based on molecular characteristics of the tumor

- **Context:**
  - Advances in many tumors culminating in large-scale sequencing
  - Development of therapies directed to at least some “driver pathways”
  - May be histology or mutation specific
FOCUS 4: first-line mCRC, fit for chemo, excluding pts >400K, consent for biomarker analysis

Any standard chemo x 16 wks

Biomarker panel:
- B-RAF, K-RAS, N-RAS mutations
- Ereg, DUSP4/6 mRNA, PTEN, DNA repair IHC

Response or SD at 16 wks
Consent for stratified randomisation

Response or SD at 16 wks

- B-RAF mutation
  - P
    - B-RAF inhibitor (GSK)
  - R
    - B-RAF + MEK inhibitors (GSK)

- K-RAS, N-RAS mutation
  - P
    - Dual pathway inhibition PI3K + MEK (AZ?)
  - R
    - Dual pathway inhibition PI3K + MEK (GSK)

- EGFR dependant
  - P
    - Pan-HER TKI (AZ?)
  - R
    - Parp Inhibitor (Clovis?)

- DNA repair deficient
  - P
    - No Rx
  - R
    - Capecitabine

Unclassified or when other stratifications temporarily closed

Stage II/III Primary outcome measure: PFS from randomisation to interval therapy (recommence 1st-line chemo)

Decision points for each stratified cohort:
- 1st and 2nd and 3rd interim analyses for Lack of Activity (PFS)
- 4th analysis for PFS efficacy (target HR = 0.5 for B-RAF<sup>mut</sup>, all others 0.65)

- For biomarker-selected cohorts that pass 3rd PFS Lack of Activity stage (alpha = 0.1): test specificity of biomarker selection in a separate cohort of patients without the selection biomarker
- For larger cohorts that pass 4th Efficacy PFS stage: Continue phase III, with final efficacy analysis on OS endpoint
Shiva Trial
PI: C. Le Tourneau
Sponsor: Institut Curie

Patients with refractory cancer (all tumor types) → Informed consent signed → Tumor biopsy + Blood sample → High Throughput Sequencing → Molecular profiling → Informed consent signed → Eligible patient

Non eligible patient → Molecular biology board → Specific therapy available

Conventional therapy based on oncologist’s choice
- Chemotherapy
- Hormone therapy
- Clinical trial with drug(s) of interest

Specific therapy available → YES

Therapy based on molecular profiling
- Approved molecularly targeted agent (single agent or combination if relevant)
NCI-MATCH

- Umbrella protocol for multiple, single-arm phase II trials
  - Each molecular subgroup matched to a targeted agent
- IND for protocol template
  - Arms could be added or deleted without affecting other arms
- Initially focused on single-agents (commercial or experimental)
  - Combinations will be considered for targets that have validated combination targeted therapy
  - Need minimum dose/safety established in phase 1 trials
- Study will be reviewed by the CIRB
Adaptive Designs

- Randomize between at least 2 arms within biomarker-defined strata
  - Different signatures, different allowed drugs
- Evaluate success in an ongoing manner
  - Alter randomization ratio?
- Drop poor performers
- ‘Graduate’ good performers to phase III trials
- Examples: ISPY-2 (Breast), BATTLE (NSCLC)
ISPY-2 Adaptive Design
Learn, Drop, Graduate, and Replace Agents Over Time

Patient is on study*

Key
MRI
Residual Disease (Pathology)

Randomize

Paclitaxel + Trastuzumab
Paclitaxel + Trastuzumab* + New Agent A
Paclitaxel + Trastuzumab* + New Agent B
Paclitaxel + Trastuzumab* + New Agent F

AC → Surgery

Randomize

Paclitaxel
Paclitaxel + New Agent F
Paclitaxel + New Agent GH
Paclitaxel + New Agent E

AC → Surgery

*Investigational agent may be used in place
Conclusions

• Targeted therapies, biomarkers require new methods for trials
  • Endpoints
  • Trial designs

• Fundamental principles still valid
  • Randomization
  • Rigorous design

• Trials will become smaller
  • By necessity (rare tumors)
  • By design (expected larger effects)
  • By strategy (?) – take more risks, bigger long-term rewards