Statistical and practical considerations for cancer clinical trials designed to evaluate novel biomarker-guided therapies

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Disclosures

• Nothing to disclose
“Drivers”

- A number of molecular alterations have been shown to be critical for maintenance of malignant phenotype
- These drivers, though uncommon, may be susceptible to inhibition with targeted drugs, resulting in remarkable responses in refractory tumors
- Examples:
  - EGFR: erlotinib/gefitinib & other EGFR TKIs in NSCLC
  - ALK: crizotinib in NSCLC
  - BRAF: vemurafenib in melanoma
Coordinated Approaches

• Prospective therapy trials based on high content molecular characterizations of tumors
• Retrospective discovery through comprehensive molecular analysis of stored tumor specimens from “exceptional responders”
Prospective Genomic Trials

- Biomarker-based therapy signal-finding (non-randomized, phase Ib/II)
- Biomarker-based therapy efficacy evaluation (randomized, phase II or III)
- Biomarker-strategy vs. standard therapy (phase II or III)
  - All-comers
  - Enriched
Umbrella Trials

- Common entry point for patients
- Molecular profiling of tumors
- Evaluate multiple molecularly-guided therapies
- Parsimonious use of specimens, high throughput assays
- Potential for master protocols and INDs to cover multiple therapeutic agents
- Potential to coordinate regulatory requirements for multiplex assays (CLIA, FDA IDEs or submissions)
Multiple-Biomarker Signal-Finding Design

- Multiple single arm studies; ORR, PFS, or SD endpoint
- Can’t assess off-target effects or prognostic effects
- Refinement outside of biomarker-positive groups difficult
- Overlapping biomarkers: Randomize? Prioritize?
- Definition of “success” in setting of mixed histologies and prognostic effects?
Multiple-Biomarker Randomized Design

- Multiple randomized biomarker-enrichment designs; PFS, DFS or OS (preferably) endpoint
- Controls for prognostic effects; can’t assess off-target effects
- Refinement outside of biomarker-positive groups difficult
- Overlapping biomarkers: Randomize? Prioritize?
- Meaningful treatment effect in context of mixed histologies?
Biomarker-Strategy Design (All-Comers)

- Inefficient: Biomarker-negative treatment same on both arms
- Well-suited for complex multi-biomarker guided treatment
- Refinement outside of biomarker-positive groups difficult
- Must measure biomarkers in non-guided arm to distinguish prognostic effects from therapy benefit
- May obscure effective or ineffective agents in global test

(R = randomization)

Diagram:
- All patients
- R
  - All biomarkers measured
  - Positive for ≥ 1 biomarker → Tailored agent combination
  - Negative for all biomarkers → Control therapy
- Non-guided Control therapy

Control therapy
All patients
All biomarkers measured
Positive for ≥ 1 biomarker
Negative for all biomarkers
Tailored agent combination
Control therapy
Non-guided Control therapy
Biomarker-Strategy Design (Enriched)

- Requires biomarker measurements on all patients
- Well-suited for complex multi-biomarker guided treatment
- Refinement outside of biomarker-positive groups difficult
- Can’t fully assess off-target effects of experimental agents
- Randomization controls for prognostic effect within subgroup
- May obscure effective or ineffective agents in global test

(R = randomization)
Additional Design Options

• Adaptive* features
  – Interim monitoring (almost always do this)
  – Seamless Phase II/III
  – Dropping underperforming arms or biomarker subgroups
  – Outcome dependent randomization ratio
  – Bayesian approaches

• Randomization of biomarker-negative patients to experimental agents to evaluate off-target effects (if no other known effective therapies available and toxicities minimal)

Design Challenges

• Choice of endpoint (cytotoxic vs. cytostatic, beware of prognostic effects)
• Duration of targeted therapy
• Extension to tailored combination therapies with a multiplicity of potential toxicities and ever smaller patient populations
• Multiple histologies (same marker in different context)
• Choice of biomarkers and assays and their reproducibility
• Prioritization of overlapping biomarker subsets
Mean single-nucleotide variants (SNV) concordance over 15 exomes between five alignment and variant calling pipelines

(Figures 1 A&C from O’Rawe et al, Genome Medicine 2013, 5:28)
Logistical Challenges

• Agents from multiple companies
  – Targeting same molecular characteristics
  – Used in combination against simultaneously occurring distinct alterations

• Competing trials

• Adequate availability of promising agents/biomarkers

• Getting the patients to where the trials are
Collaboration & Cooperation

- Harmonize data collection in existing trials
- Fewer, more widely accessible trials

... or we risk drowning in umbrella trials
Molecular Analysis for Therapy Choice (NCI MATCH)

- Multiple-Biomarker Signal-Finding Design
  - One protocol with multiple single arms, nonrandomized
- Network of CLIA labs
  - Targeted panel of mutations/amplifications for eligibility
  - Whole-exome sequencing, baseline & progression for research
  - Established comparability
- Collaboration with multiple drug companies
  - Initially single-agents (approved or investigational)
- Screen approx. 3000 patients to accrue 1000 for molecularly guided therapy
NCI MATCH Eligibility

- Solid tumors which have progressed following at least one line of standard therapy
- Exclude histologies from a given arm if already FDA approved for that indication or lack of efficacy documented
- Tumor accessible for biopsy and patient willing to undergo biopsy
- At least 18 years of age
- Performance status ECOG 0-2
- Adequate organ function
NCI MATCH Logistics

- ECOG-ACRIN to lead with full cooperation of U.S. NCI Clinical Trials Network (NCTN)
- Also available through Cancer Trials Support Unit (CTSU) and Clinical Community Oncology Program (CCOP)
- IND for umbrella protocol template
- Central IRB
- Projected launch date: mid-to-late 2014
NCI Exceptional Responders Initiative

• “Exceptional response” definition
  – CR or PR lasting ≥ 6 months
  – Drug did not gain FDA approval in that indication due to insufficient activity (e.g., ORR=CR+PR<10% in early trials)

• Tissue
  – Tissue (≥ 50% tumor, FFPE), prefer just prior to drug treatment
  – Normal tissue desirable

• Goal: 100 analyzable tissues for whole exome sequencing; possibly data only from 100-200 additional cases
  – Approx. 80 potential cases identified in CTEP-IND trials database

• Under intensive development for early 2014 launch

• Contact: NCIExceptionalResponders@mail.nih.gov