NCPF Workshop on Contemporary Issues in Human Subject Protections in Cancer Research

Session 6: Challenges in Studies with Multiple IRBs

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My Perspective

- 30 year career as academic clinical researcher
- Former Associate Dean for Clinical Research, University of Chicago
- Former Group Chair, Cancer and Leukemia Group B

Challenge Depends on Perspective

- Sponsor
- PI
- Institution
- Local IRB
- Research participant

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Issues

- Efficiency of study launch
- Delay in participation/enrollment for time sensitive studies
- Redundancy of review when few changes permitted
- Variable quality/extent of local IRB review might diminish information transfer/increase risk to participants

Issues

- Increased length/complexity of consent form following local review
- No standard metric to define the "quality" of an IRB review
- Changing recruitment model for biomarker-driven trials

Empirical Research

- Literature review by Check, et. al*. identified 11 empirical studies on IRB review of multi-center studies *(*Clinical Trials 10:560,2013)*
- Ravinia, et. al.: average of 5.2 changes made/site, no substantive changes to protocol, estimated cost of local review $107,544
- Stark, et.al.: 16/18 IRBs had changes to IC, 7/18 IRBs had no concerns with protocol but 9 had at least 1 major concern
- Burman, et. al.: 25 sites, no changes made to protocol as a result of local review, median of 46.5 changes made to ICs of which 82.5% changed wording without meaning, median time to approval 104.5 days

Empirical Research

- Silverman, et.al.: analysis of 16 sites in a multi-center trial, only 3/16 ICs contained all required elements, reading levels ranged from grades 8-13.
- Conclusion from all studies: local IRB review of multi-center studies highly variable; changes to protocol rare; changes to IC might introduce mis-information; much time and effort consumed
- Wagner, et. al.: NCI CIRB associated with faster reviews (34 days), less staff effort (6 hours), reduced cost.

The Paradoxical Problem with Multiple IRB Review

- Multiple IRB reviews diffuse responsibility potentially leading to more superficial review
- No IRB feels empowered to change the protocol
- Substantive problem with the protocol may not be communicated as site simply does not participate
- Consent forms likely compliant with regulatory/ethical standards and local changes can introduce errors or confusion
- Substantive problems might not be communicated

Menikoff, NEJM 363:1591, 2010

Challenges for Stakeholders

Sponsor and PI

- Efficiency of study start-up
- Workload required to meet needs of all sites
- Obligation to address/communicate site concerns
- Need to track variable regulatory documents across sites

Local IRB

- Time/effort/cost of review
- Obligation to protect local participants
- Concerns about institutional liability
- Temptation to make unnecessary changes
- Lack of awareness of experiences/concerns at other sites

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Challenges for Research Participants

- Has there been a “good quality” IRB review?
- Have they gotten complete/accurate/understandable information about risks/benefits?

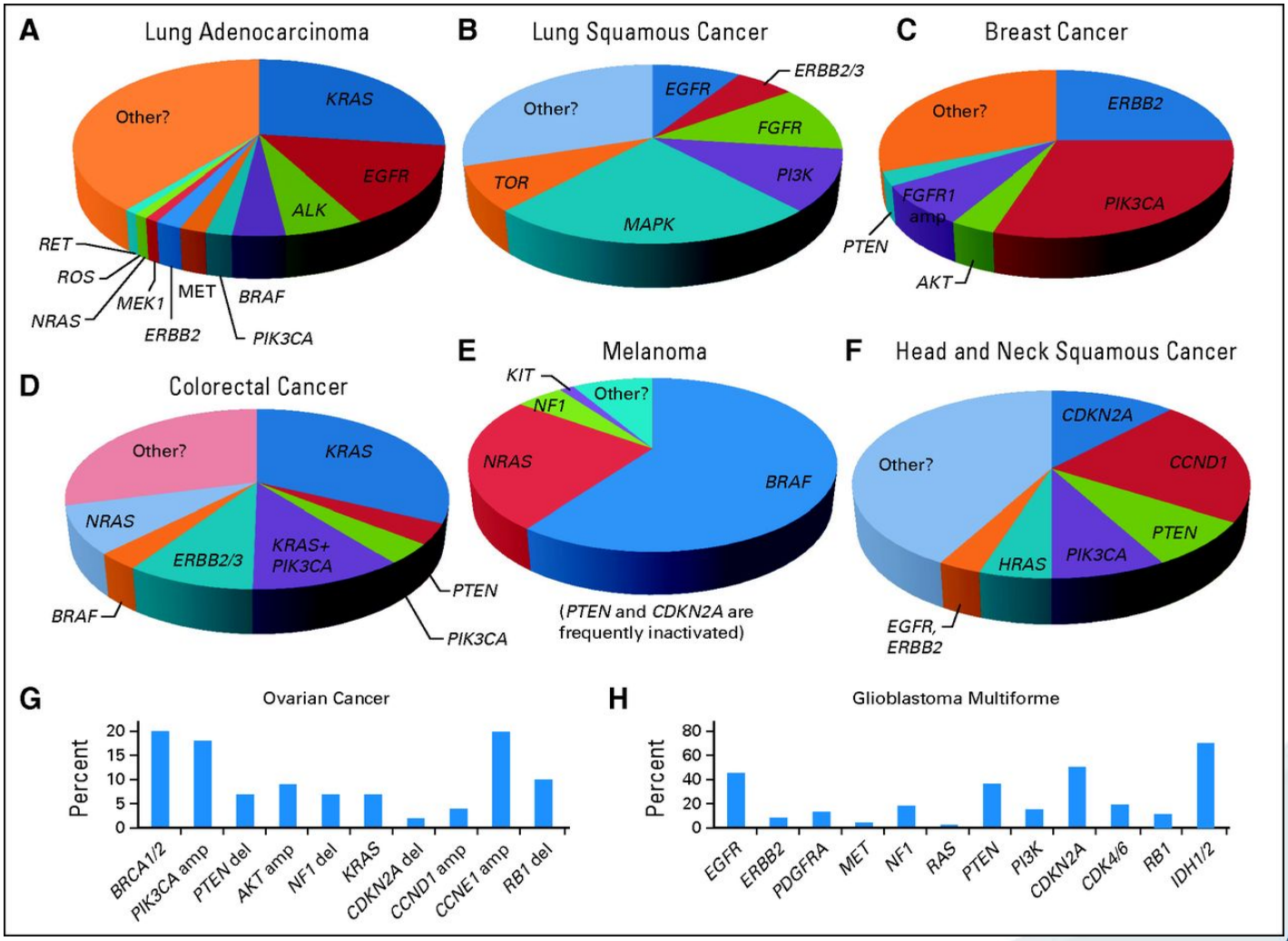
Challenges for Research Participants

- Are they getting the same information as participants at other sites?
- Might they miss an opportunity to participate if their site declines protocol?

IRB Review in the Era of Genomic Medicine

- Need to identify patients with rare genomic subtypes
- Impractical to seek local IRB review at multiple sites for occasional patients
- Does every local IRB have the expertise necessary to review these studies?

Genomic Alterations in Common Solid Tumors



Garraway L A JCO 2013;31:1806-1814

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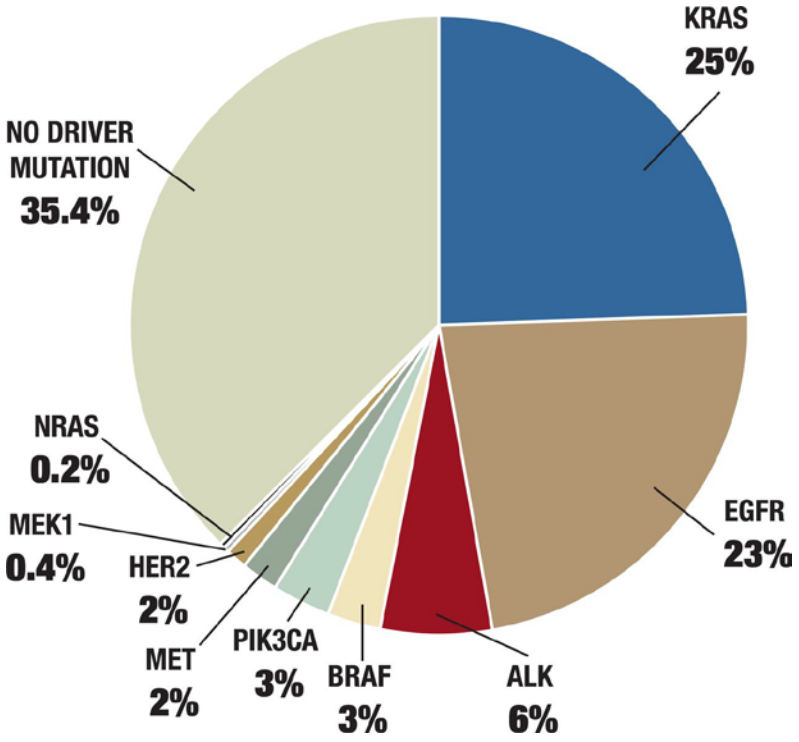
Matching Drugs to Mutations



Genotypes of NSCLC

Clin Cancer Res 18 (Suppl 1) S67. Nov 1, 2012

Potential Treatments

- Crizotinib (ALK TKI)
- Erlotinib (EGFR TKI)
- Lapatinib, Afatinib (EGFR/HER2)
- Onartuzumab (MetMAb)
- Tivantinib (cMET TKI)
- Selumetinib (MEK1/2)
- Trametenib (MEK1/2)
- Vemurafenib (BRAF)

Trial Strategies

- Enroll all patients in screening protocol; capture characteristics to enable better phenotype definition; refer screen+ patients to clinical trials; provides “pre-qualified” pool of patients
- Test patients outside protocol setting; enroll only patients with required biomarker in therapeutic trial

IRB Review in the Era of Genomic Medicine

- Need to deliver trial to patient, not patient to trial
- Approach requires CIRB as individual IRB review impractical and costly for number of trial participants expected at each site

Conclusions

- Little is gained from individual site review in multi-center studies.
- Potential for multi-site review to actually increase risk and diminish quality of information conveyed to research participants
- Recruitment in the genomic era only practical with CIRB
- Need a regulatory framework that encourages site acceptance of central IRB review
- Need additional research on appropriate metrics to define “quality” of IRB review