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The Role of Non-Randomized Trials for the Evaluation of Oncology Drugs
The Role of Non-Randomized Trials for the Evaluation of Oncology Drugs

Deborah Armstrong, MD
Johns Hopkins Kimmel Cancer Center
Panel One: Potential Strategies for Non-Randomized Evaluation of New Drugs

- Panel members
- Introduction and Historical Perspective
- Single Arm Trials
- Use of Objective Response Rate
- Randomized and Non-randomized Clinical Trials
Speakers

- Deborah Armstrong, MD, Johns Hopkins Kimmel Cancer Center
- Mace Rothenberg, MD, Pfizer Inc
- Gideon Blumenthal, MD, FDA
- Richard Simon, D.Sc., National Cancer Institute
- Josh Sommer, Chordoma Foundation
- Richard Pazdur, MD, FDA

*Contributor:* Lisa LaVange, PhD, FDA
Non-Randomized Trials for the Evaluation of Oncology Drugs: Historical Perspective

• 1962 Kefauver-Harris Drug Amendments to FD&C Act required informed consent and AE reporting
  – No requirement for comparative efficacy

• FDA approved oncology drugs largely on the basis of tumor response through the 1980’s

• ODAC recommended improvement in survival or patient symptoms
Single Arm Trials

• Single arm trials are commonly the basis for accelerated approvals of oncology drugs

• Benefits
  – Require fewer resources
  – Take less time to complete
  – Appropriate in refractory populations
  – Easily understood by the target patient population

• Limitations
  – Defined study population frequently not comparable to historic controls
  – If response rate is marginal it may not reflect true clinical benefit
  – Poor characterization of safety (drug vs. disease)
Objective Response Rate (ORR)

- Early signal of efficacy
- Used commonly in clinical practice
- Benefit of ORR accepted by patients and providers
- Important additional factors: duration of response, number of CRs, volume of disease, sites of response (e.g. visceral vs. nodal vs. cutaneous)
- May be used in a single-arm trial: the ORR presumed to be zero in untreated malignancy
- May not always reflect true clinical benefit
  - Does not account for stable disease, improvement in non-measurable disease or in disease-related symptoms
Randomized Clinical Trials

- Minimize bias
  - When well designed will optimize comparability of treatment arms
- Can document OS advantage
  - “Gold Standard” for clinical benefit
  - Priority for patient population
- Optimal for documenting safety and toxicity of experimental treatment
- Commonly required for full FDA approval
Limitations of Randomized Clinical Trials

- Excessive time to accrue to a RCT
  - Rare Cancers
  - Low-frequency, molecularly defined subsets of common cancers

- Strong potential for benefit of study agent
  - Patient dropout on control arm (unblinded studies)
  - Crossover within or external to study
  - Ethical challenge?
Situations in which randomized trials may not be feasible or ethical:

• New drug with very strong biological rationale in a biomarker-selected population of patients

• New drug demonstrates unprecedented ORR in a setting of high unmet need with no effective therapies

• An already approved molecularly targeted agent is being tested in a rare tumor histology expressing the appropriate biomarker
Characterizing Extraordinary Activity in Early, Non-Randomized Trials: The Crizotinib Experience

Mace Rothenberg, MD
Pfizer, Inc
Situations in Which Single Arm Trials Could Potentially Support Full Approval

• An unprecedented effect on ORR is observed in a setting of high unmet medical need
• Clinical trial patients have been well characterized enabling target population to be clearly defined
• Experience exists in a sufficient number of patients to allow adequate assessment of risk:benefit relationship
• A proper (historical) context can be provided
Identification of the transforming **EML4–ALK** fusion gene in non-small-cell lung cancer

Manabu Soda\(^1\), Young Lim Choi\(^1\), Munehiro Enomoto\(^1\), Shuji Takada\(^1\), Yoshihiro Yamashita\(^1\), Shunpei Ishikawa\(^2\), Shin-ichiro Fujiiwara\(^1\), Hideki Watanabe\(^1\), Kentaro Kurashina\(^1\), Hisashi Hatanaka\(^1\), Masashi Bando\(^1\), Shoji Ohno\(^1\), Yuichi Ishikawa\(^2\), Hiroyuki Aburatani\(^2\)*, Toshiro Niki\(^1\), Yasunori Sohara\(^1\), Yukihiko Sugiyama\(^2\) & Hiroyuki Mano\(^3\),

A mouse model for **EML4-ALK**-positive lung cancer

Manabu Soda\(^4\)\(^5\), Shuji Takada\(^4\), Kengo Takeuchi\(^4\), Young Lim Choi\(^4\), Munehiro Enomoto\(^4\), Toshio Ueno\(^4\), Hidenori Haruta\(^4\), Toru Hamada\(^4\), Yoshihiro Yamashita\(^4\), Yuichi Ishikawa\(^4\), Yukihiko Sugiyama\(^4\), and Hiroyuki Mano\(^4\)

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**A**

![Graph showing survival comparison between treatment and control groups](image)
Anaplastic Lymphoma Kinase Inhibition in Non–Small-Cell Lung Cancer

Eunice L. Kwak, M.D., Ph.D., Yung-Jue Bang, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D., Alice T. Shaw, M.D., Ph.D., Benjamin Solomon, M.B., B.S., Ph.D., Robert G. Maki, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph.D., Bruce J. Dezube, M.D., Pasrija Jänne, M.D., Ph.D., Daniel B. Costa, M.D., Ph.D., Marileila Varella-Garcia, Ph.D., Woo-He Kim, M.D., Thomas J. Lynch, M.D., Panos Fidias, M.D., Hannah Stubbs, M.S., Jeffrey A. Engelman, M.D., Ph.D., Lecia V. Sequist, M.D., M.P.H., WeiWei Tan, Ph.D., Leena Gandhi, M.D., Ph.D., Mari Mino-Kenudson, M.D., Greg C. Wei, Ph.D., S. Martin Shreeve, M.D., Ph.D., Mark J. Ratain, M.D., Jeffrey Settleman, Ph.D., James G. Christensen, Ph.D., Daniel A. Haber, M.D., Ph.D., Keith Wilner, Ph.D., Ravi Salgia, M.D., Ph.D., Geoffrey I. Shapiro, M.D., Ph.D., Jeffrey W. Clark, M.D., and A. John Iafriate, M.D., Ph.D.
Clinical Features and Outcome of Patients With Non–Small-Cell Lung Cancer Who Harbor EML4-ALK

Situations in Which Single Arm Trials Could Potentially Support Full Approval

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Crizotinib - Discovery to FDA Approval

Rapid Timeline from Compound Identification, Target Discovery and Clinical Results

The *Project Data Sphere*® Initiative

- Independent, voluntary, not-for-profit initiative of the CEO Roundtable’s Life Sciences Consortium
- One place to broadly share, integrate, & analyze cancer trial data
  - from academic and industry Phase III clinical trials
  - historical, comparator arm data
  - raw anonymized patient level data, data dictionary, protocols and CRFs
- State of the art analytic tools provided by SAS

www.ProjectDataSphere.org
Executive Dashboard
4/8/14 (Launch) – 10/31/14

User Demographics

% of Users by Job Function

- N/A, Other
- Data Mgmt/Programmer
- Biostatistician
- Oncologist
- Basic Scientist
- Multiple
- Pharmacologist
- Epidemiologist

% of Users by Industry/Sector

- Pharma/Biotech
- Academia
- Other
- Tech/Service Provider
- Non-Profit
- Clinical Practice
- Government

% of Users by Geography

- N. America
- Europe
- Asia
- S. America
- Australia

Patient Lives by Data Provider

In Platform & In Preparation

To Achieve our Goal:

- In Preparation: 5,000
- In Platform: 10,000
- At Launch: 4,000

Progress to 25,000 Patient Lives Target

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<td>Bayer</td>
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<td>MD Anderson</td>
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<td>J&amp;J</td>
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Key Metrics

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Project Spotlight

The first publication using data from the Project Data Sphere initiative was presented at the Prostate Cancer Foundation’s Scientific Retreat by Dr. Anthony Joshua of the Princess Margaret Cancer Center. Dr. Joshua presented his analysis on “Defining the Mechanism and Application of Metformin and Statin therapy in Prostate Cancer.” A manuscript is in preparation for submission to a peer-reviewed journal.
The Role of Non-Randomized Trials for the Evaluation of Oncology Drugs

Gideon Blumenthal, MD
FDA
High magnitude and durable Overall Response Rates (ORR) in single arm trials in oncology

• Used for accelerated approval (lack of available therapies, high unmet medical need)

• Many transformative therapies in oncology in the past few decades have shown large and durable ORR in early clinical development
  – Usually in targeted, molecularly enriched populations

• When is ORR suitable for “traditional” approval?
  – As direct clinical benefit?
    • As an oncologist, response is a key metric we use to refer patients to clinical trials or standard of care
  – As an established surrogate?
Challenges with “old paradigm”

No molecular enrichment

- p53
- MET
- RO1
- KRAS
- EGFR
- ALK

Platinum doublet

Platinum doublet + drug X

HIGH RISK PHASE 3 FAILURE OR CLINICALLY SMALL EFFECT

Challenges with “new paradigm”

molecular enrichment

Targeted Therapy

ALK

Large effect on durable ORR

N=100-200

- Low frequency subsets in even common cancers => high screen failure rate
- Large effect on response in early clinical studies: is there clinical equipoise to conduct a randomized study?
When are randomized trials unnecessary?

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

BMJ 2003; 327:1459

Large effects vs. historic control
- Penicillin for CAP
- Insulin for diabetes
- Multi-agent chemo for testicular cancer
Why large and durable overall response rates?

• **Directly attributable** to a drug’s effect as spontaneous regression of cancer is extremely rare
• Why not PFS and OS in single arm trials?
  – difficult to discern drug effect from patient and disease natural history

Vismodegib Response
Von Hoff et al., NEJM, 2009; 361: 1164-72
Responses can quantitatively and qualitatively differ

Response seen from across the room

Response where you need an arrow to point it out

Bergethon et al., JCO, 2012; 30(8): 863-70

Butrynski et al., NEJM, 2010; 363: 1727-1733
Overall Response Rate as a potential surrogate for Progression-Free Survival: A meta-analysis of metastatic non small cell lung cancer trials submitted to the U.S. Food and Drug Administration

Gideon Michael Blumenthal, Stella Karuri, Sean Khozin, Dickran Kazandjian, Hui Zhang, Lijun Zhang, Shenghui Tang, Rajeshwari Sridhara, Patricia Keegan, Richard Pazdur

Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Presented at Clinical Science Symposium: “Targeting EGFR- The Next Ten Years”, ASCO 2014
## Non small cell lung cancer (NSCLC) meta-analysis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Control Arm</th>
<th>Design</th>
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<th>Patient Population</th>
<th>Primary Endpoint</th>
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<tr>
<td>Crizotinib</td>
<td>Pem (or doc)</td>
<td>Head-to-Head</td>
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<td>2L ALK+</td>
<td>PFS (IRC)</td>
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<td>Afatinib</td>
<td>Cis + pem</td>
<td>Head-to-Head</td>
<td>345</td>
<td>1L EGFRm</td>
<td>PFS (IRC)</td>
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<td>Erlotinib</td>
<td>Cis(car) + doc (gem)</td>
<td>Head-to-Head</td>
<td>174</td>
<td>1L EGFRm</td>
<td>PFS (INV)</td>
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<tr>
<td>Nab-pac + car</td>
<td>Car + pac</td>
<td>Head-to-Head</td>
<td>1052</td>
<td>1L</td>
<td>ORR (IRC)</td>
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<tr>
<td>Cetuximab</td>
<td>Cis + tax</td>
<td>Add-On</td>
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<td>PFS (IRC)</td>
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<td>1125</td>
<td>1L</td>
<td>OS</td>
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<tr>
<td>Vandetanib</td>
<td>Erl</td>
<td>Head-to-Head</td>
<td>1240</td>
<td>2L+</td>
<td>PFS (INV)</td>
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<tr>
<td>Vandetanib</td>
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<td>Add-On</td>
<td>534</td>
<td>2L+</td>
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<td>Vandetanib</td>
<td>Doc</td>
<td>Add-On</td>
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<td>PFS (INV)</td>
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<td>Gefitinib</td>
<td>Doc</td>
<td>Head-to-Head</td>
<td>1466</td>
<td>2L+</td>
<td>OS (INV)</td>
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<td>Bevacizumab</td>
<td>Cis + gem</td>
<td>Add-On</td>
<td>692</td>
<td>1L NSq</td>
<td>PFS (INV)</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Cis + gem</td>
<td>Add-On</td>
<td>698</td>
<td>1L NSq</td>
<td>PFS (INV)</td>
</tr>
<tr>
<td>Pemetrexed + cis</td>
<td>Cis + gem</td>
<td>Head-to-Head</td>
<td>1725</td>
<td>1L</td>
<td>OS (INV)</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Car + pac</td>
<td>Add-On</td>
<td>850</td>
<td>1L NSq</td>
<td>OS</td>
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<tr>
<td>Pemetrexed</td>
<td>Doc</td>
<td>Head-to-Head</td>
<td>571</td>
<td>2L</td>
<td>OS (INV)</td>
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</table>
Results: Trial level PFS HR versus ORR odds ratio

R-sq all trials = 0.89
R-sq trials > 500 pts = 0.77
Results: trial level associations between ORR and OS and PFS and OS

ORR and OS

PFS and OS

R-sq all trials = 0.09
R-sq trials > 500 pts = 0.44

R-sq all trials = 0.08
R-sq trials > 500 pts = 0.35
Results: patient-level responder analysis

response and PFS

response and OS

Resp vs. Non-Resp: HR=0.40 (95% CI: 0.38, 0.42)

Resp vs. Non-Resp: HR=0.40 (95% CI: 0.38, 0.43)
Conclusions

• On trial level, meta-analysis randomized, active-controlled trials submitted since 2003 indicates strong correlation ($R^2=0.89$) between ORR and PFS

• Weak or no correlation between either ORR and OS or PFS and OS
  – Possible explanations:
    • no (or weak) relationship or
    • high cross-over, under-power, long post-progression survival in the 3 small targeted therapy trials in molecularly defined populations confounds analysis

• At trial level, drug in mNSCLC subset with large effect on ORR likely to have large effect on PFS
  – Most likely to occur with molecular enrichment

• Conversely, a drug with a small effect on ORR may have small effect on PFS
Statistical Planning for Analysis of Single Arm Clinical Trials

Richard Simon, D.Sc
Chief, Biometric Research Branch
DCTD, NCI
External Controls

• A if new regimen is A+Test drug otherwise, some SOC regimen

• Need individual patient data for external control group
  • Expected to be comparable with regard to important prognostic factors (e.g. stage, prior treatment, performance status)
  • Comparable with regard to follow-up procedures and methods of response assessment
  • Need detailed complete individual patient data
  • Control group described in protocol for pivotal trial
Primary endpoint described in protocol

• Durable response
  – Response duration beyond landmark time (e.g. 6 months) likely to be more comparable that actual PFS

• Durable CR

• Survival
• Test null hypothesis that outcome distribution for patients on the test treatment is equal to that for the external controls
  – Possibly adjusted for covariates
  – Significance test uses individual patient data for the controls, not summary durable response rate
• Summary response rates ignore variability resulting from the finite size of the control group and do not permit checks for comparability
• There is a substantial statistical literature about how to plan studies that use individual patient external control groups. e.g.
Number of patients needed on test treatment
Control durable response rate .10
Test rx durable response probability .40

<table>
<thead>
<tr>
<th>m historical controls</th>
<th>Pts on test rx for power 0.90</th>
<th>Pts on test rx for power .85 with margin .05</th>
<th>Pts on test rx for power .85 with margin .10</th>
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<tbody>
<tr>
<td>50</td>
<td>33</td>
<td>60</td>
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<tr>
<td>100</td>
<td>25</td>
<td>37</td>
<td>85</td>
</tr>
</tbody>
</table>
External controls for a biomarker selected population

• Assay archived tumor tissue on a sample of control responders to estimate the fraction \( f \) of durable responders that are marker + in controls

• The overall durable response rate \( r \) in controls and the fraction \( f \) enable one to compute the posterior distribution of durable response rate for marker + patients on control rx
• m controls
• rm control responders
• sample m’ control responders with archived tissue (m’ ≤ rm) for marker assay
• fraction f of m’ are M+

\[ f = \frac{\text{prev} \times n \times p_{C^+}}{n \times p_c} \]

\[ \hat{p}_{C^+} = \frac{f}{\text{prev}} \hat{p}_c \]

e.g. \( \hat{p}_{C^+} = \frac{4/10}{.25} \times .10 = .16 \)
Posterior Probability of Control Response for M+:

RR=10/100, 4/10 responses M+,
• Perform new single arm study with n M+ patients on new treatment and obtain R durable responders

• Compute the posterior distribution of the durable response probability for the new treatment \( p_T \) and test the null hypothesis that \( p_T \leq p_{C+} \) using the estimated posterior distribution of \( p_{C+} \)

• Determine n so that the power for rejecting the null hypothesis is .80 or .90
<table>
<thead>
<tr>
<th>Control RR</th>
<th>f</th>
<th>Test rx response prob</th>
<th>n for power .85</th>
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<tbody>
<tr>
<td>10/100</td>
<td>4/10</td>
<td>.45</td>
<td>130</td>
</tr>
<tr>
<td>20/200</td>
<td>8/20</td>
<td>.45</td>
<td>40</td>
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<tr>
<td>20/200</td>
<td>8/20</td>
<td>.40</td>
<td>75</td>
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</tbody>
</table>

Prevalence M+ = .25
The Role of Non-Randomized Trials for the Evaluation of Oncology Drugs

Josh Sommer
Chordoma Foundation
The Role of Non-Randomized Trials for the Evaluation of Oncology Drugs

Richard Pazdur, MD
FDA