FRIENDS of CANCER RESEARCH

ENGELBERG CENTER for Health Care Reform at BROOKINGS

2014 Conference on Clinical Cancer Research

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November 21, 2014 • Washington, DC

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

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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

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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

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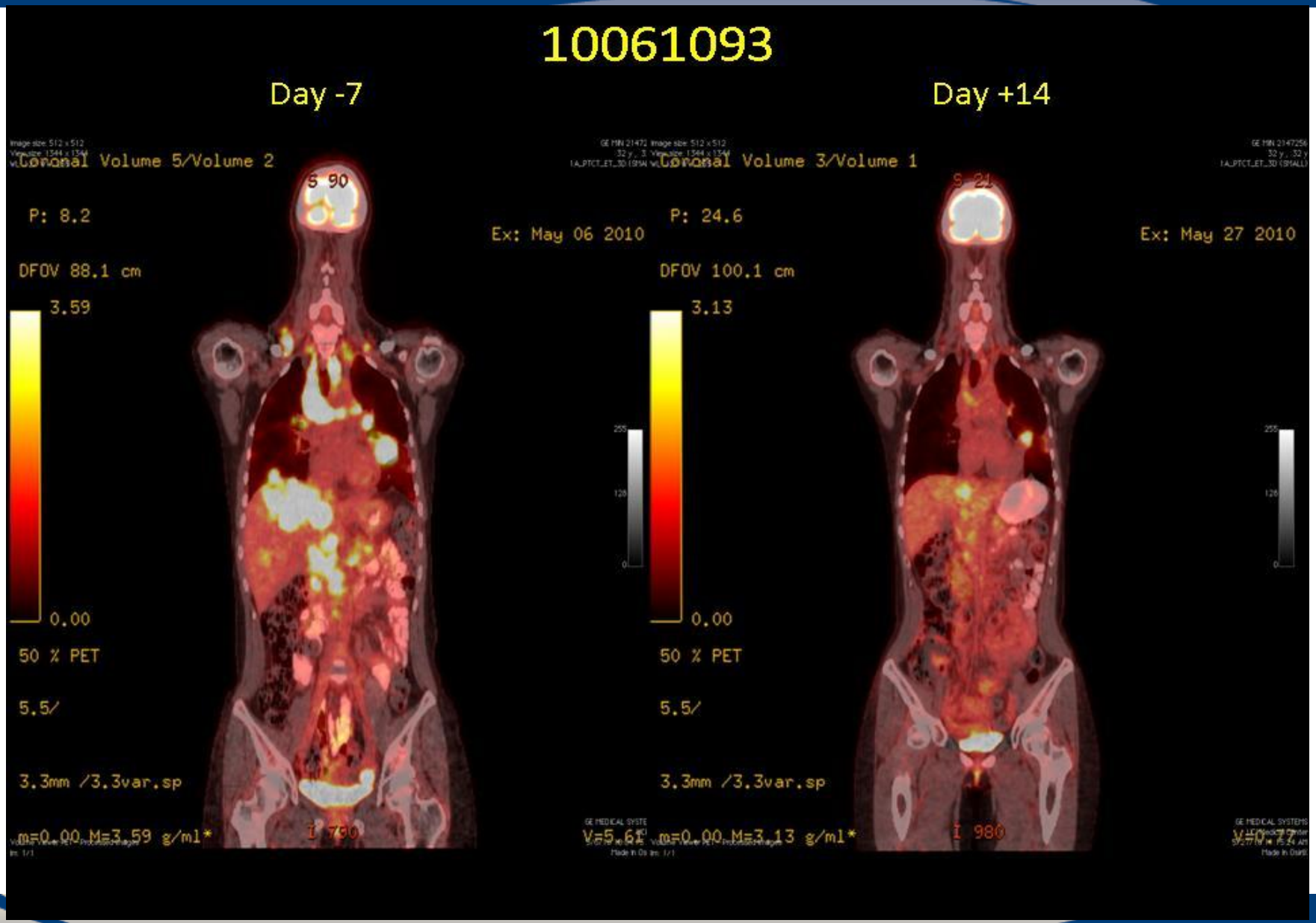
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DFOV 88.1 cm
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m=0.00 M=3.59 g/ml*
I 790
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P: 24.6
Ex: May 06 2010
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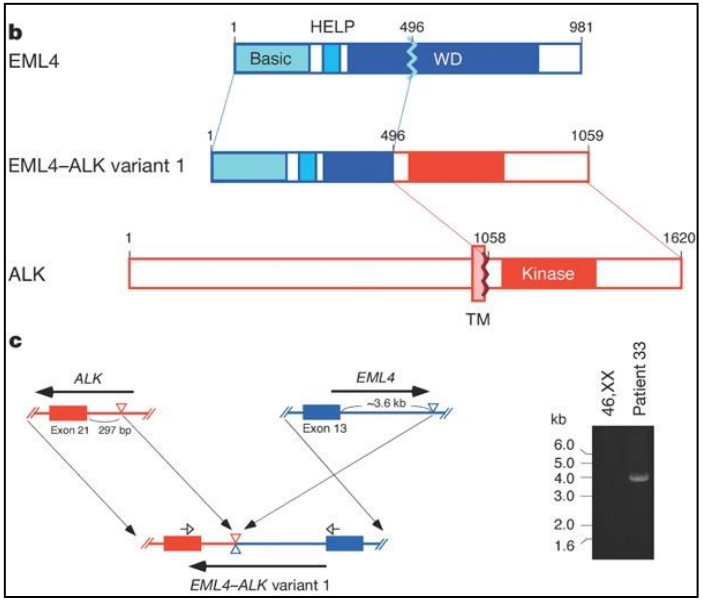
0.00
50 % PET
5.5/
3.3mm /3.3var.sp
m=0.00 M=3.13 g/ml*
I 980
Ex: May 27 2010

NATURE|Vol 448|2 August 2007

Identification of the transforming *EML4–ALK* fusion gene in non-small-cell lung cancer

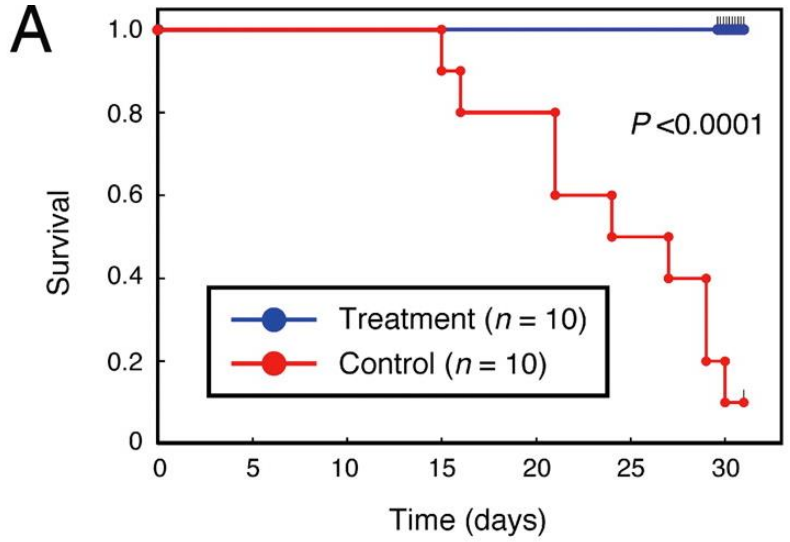
Manabu Soda[1,2], Young Lim Choi[1], Munehiro Enomoto[1,2], Shuji Takada[1], Yoshihiro Yamashita[1], Shunpei Ishikawa[5], Shin-ichiro Fujiwara[1], Hideki Watanabe[1], Kentaro Kurashina[1], Hisashi Hatanaka[1], Masashi Bando[2], Shoji Ohno[2], Yuichi Ishikawa[6], Hiroyuki Aburatani[5,7], Toshiro Niki[3], Yasunori Sohara[4], Yukihiko Sugiyama[2] & Hiroyuki Mano[1,7]



PNAS | December 16, 2008 | vol. 105 | no. 50 | 19893–19897

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

Manabu Soda[a,b], Shuji Takada[a], Kengo Takeuchi[c], Young Lim Choi[a], Munehiro Enomoto[a], Toshihide Ueno[a], Hidenori Haruta[a], Toru Hamada[a], Yoshihiro Yamashita[a], Yuichi Ishikawa[c], Yukihiko Sugiyama[b], and Hiroyuki Mano[a,d,1]

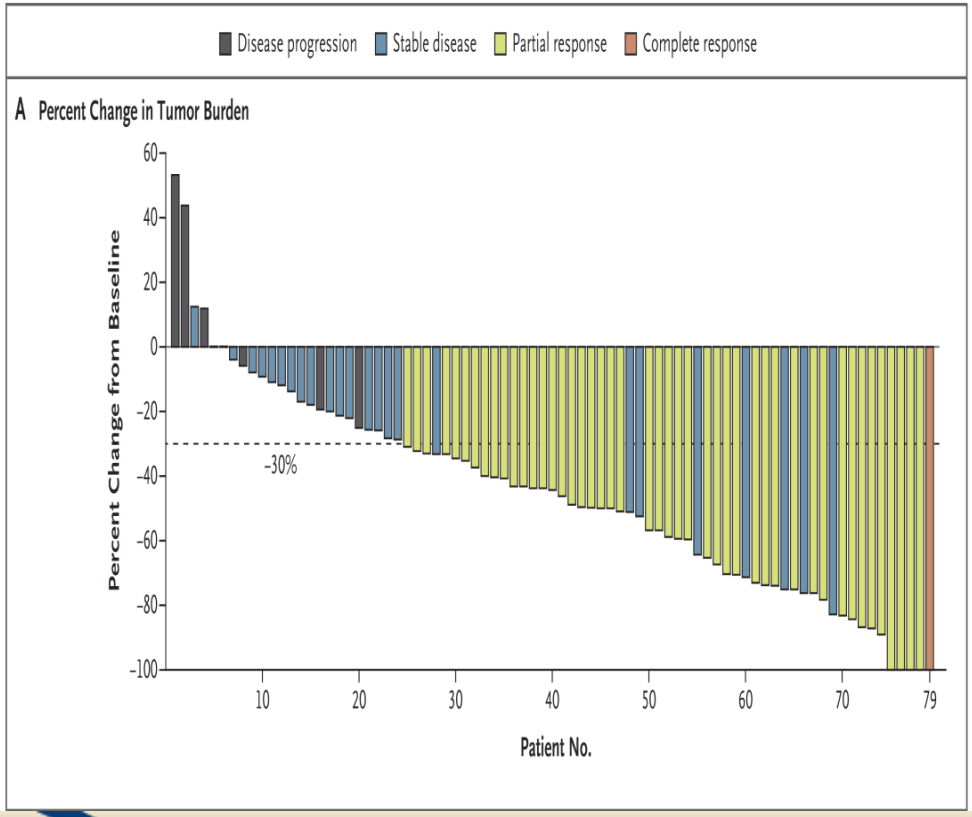


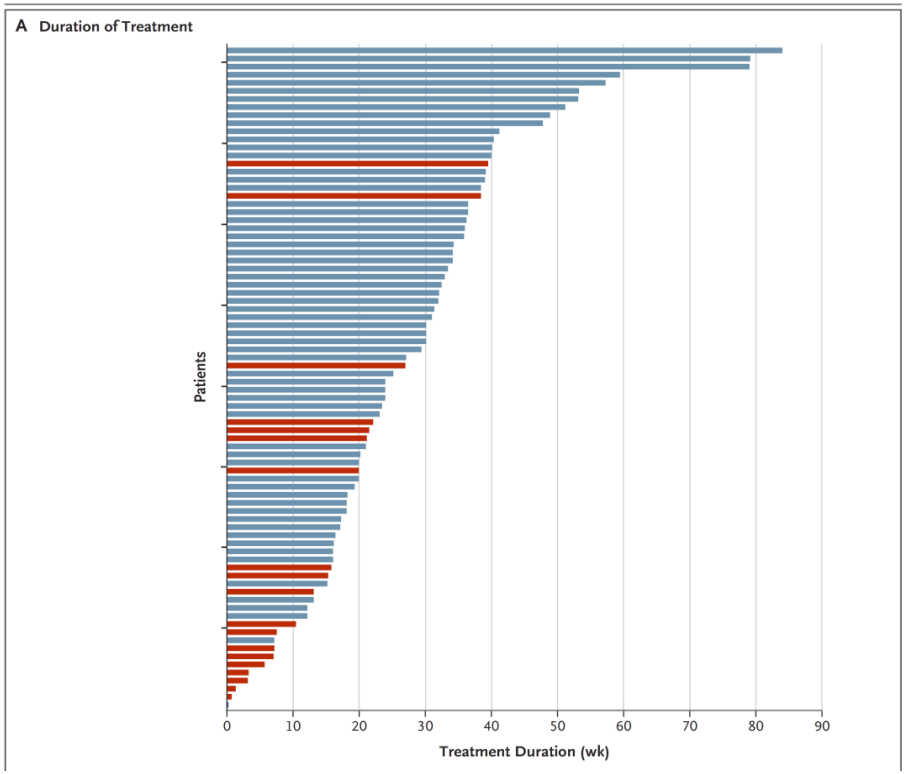
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 28, 2010 VOL. 363 NO. 18

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., Pasi A. Jänne, M.D., Ph.D., Daniel B. Costa, M.D., Ph.D., Marileila Varella-Garcia, Ph.D., Woo-Ho 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 Iafrate, M.D., Ph.D.

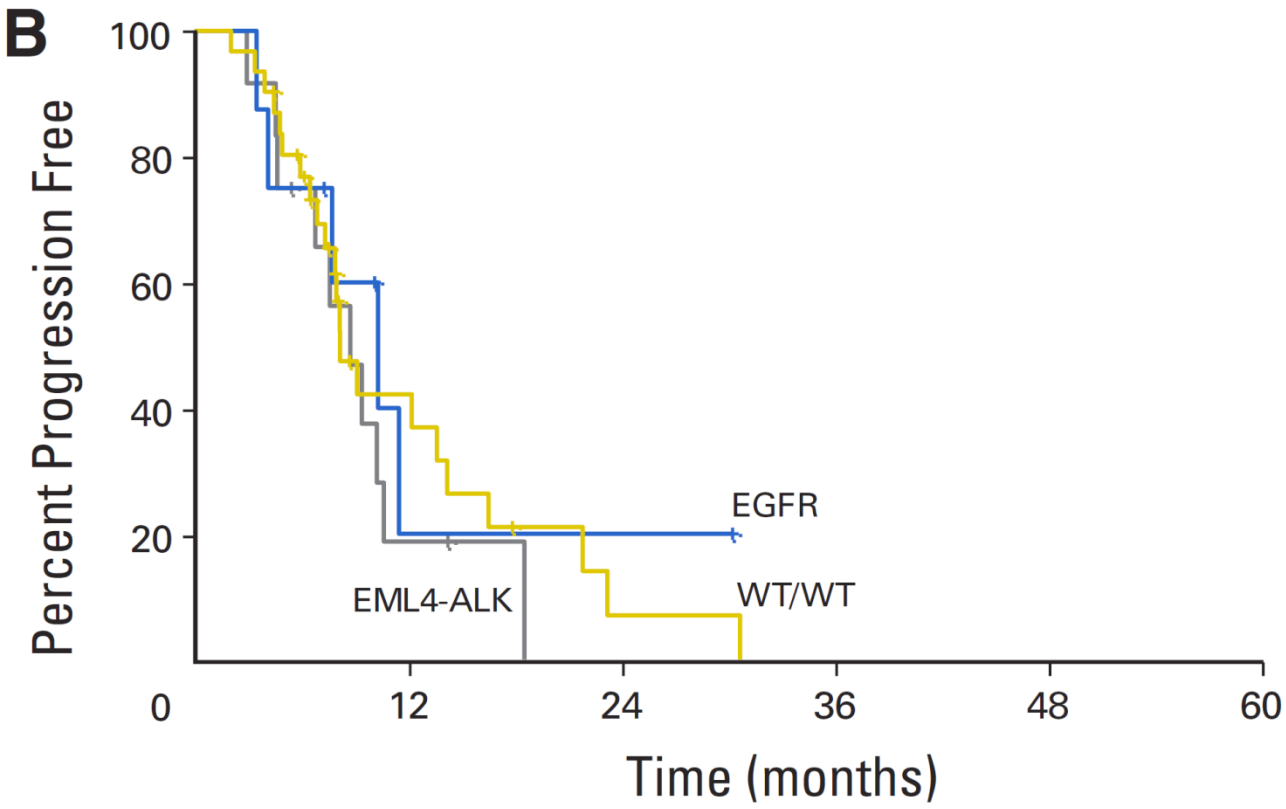




VOLUME 27 · NUMBER 26 · SEPTEMBER 10 2009
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Clinical Features and Outcome of Patients With Non–Small-Cell Lung Cancer Who Harbor *EML4-ALK*

Alice T. Shaw, Beow Y. Yeap, Mari Mino-Kenudson, Subba R. Digumarthy, Daniel B. Costa, Rebecca S. Heist, Benjamin Solomon, Hannah Stubbs, Sonal Admane, Ultan McDermott, Jeffrey Settleman, Susumu Kobayashi, Eugene J. Mark, Scott J. Rodig, Lucian R. Chirieac, Eunice L. Kwak, Thomas J. Lynch, and A. John Iafrate



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
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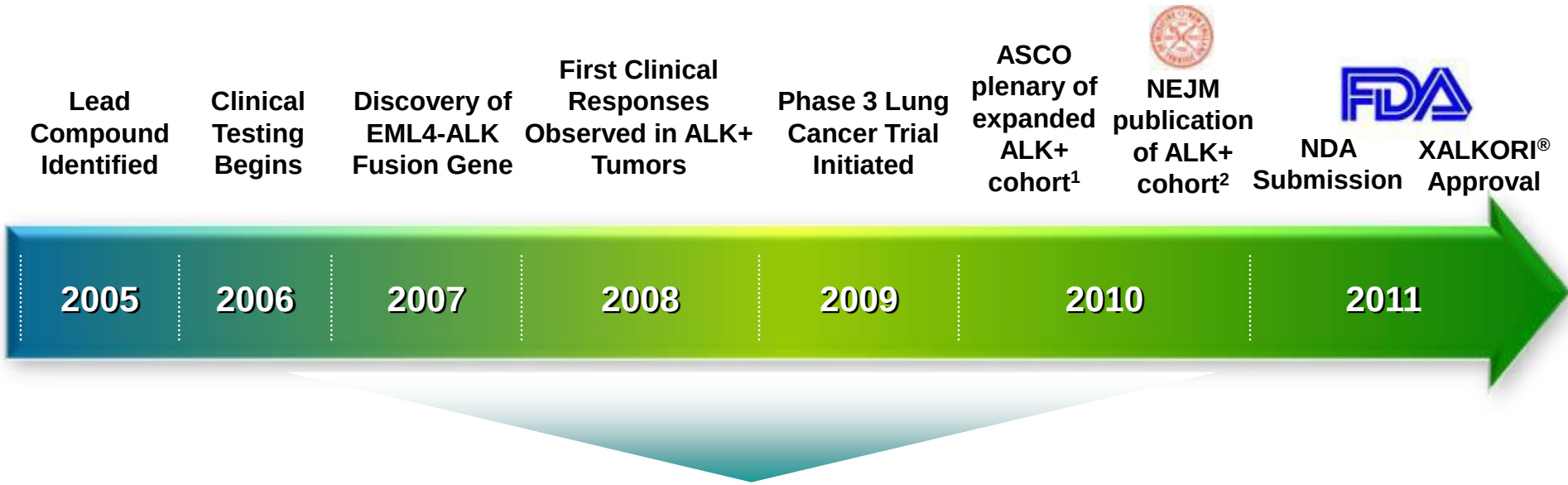
Crizotinib - Discovery to FDA Approval



Rapid Timeline from Compound Identification, Target Discovery and Clinical Results

1. Bang JY *et al*. Oral presentation at ASCO, 2010
2. Kwak et al. *New Engl J Med*. 2010;363:1693−03

The *Project Data Sphere®* Initiative

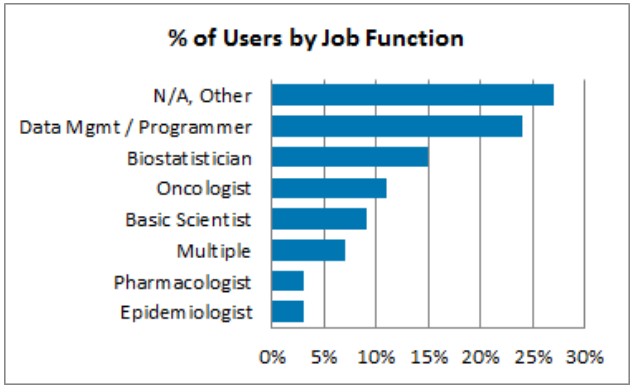
- **Independent, voluntary, not-for-profit initiative of the CEO Roundtable's Life Sciences Consortium**
- **One place to broadly share, integrate, & analyze cancer trial data**
  - **from academic and industry Phase III clinical trials**
  - **historical, comparator arm data**
  - **raw anonymized patient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

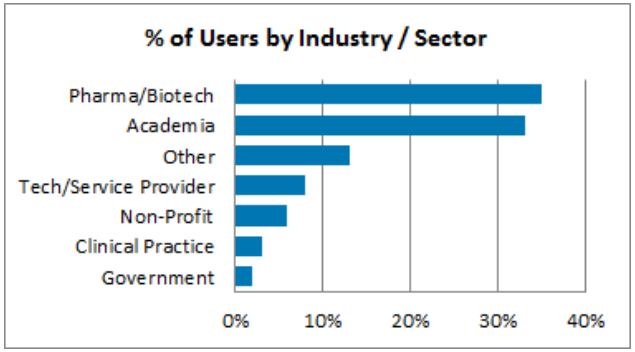
www.ProjectDataSphere.org

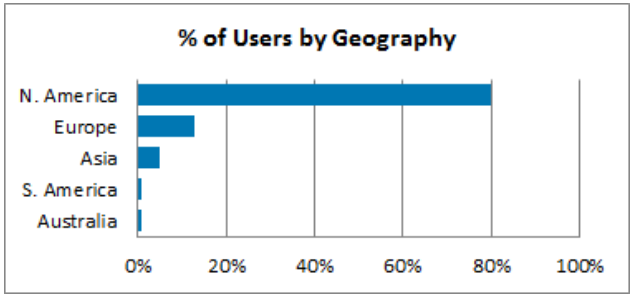
Executive Dashboard

4/8/14 (Launch) – 10/31/14

User Demographics

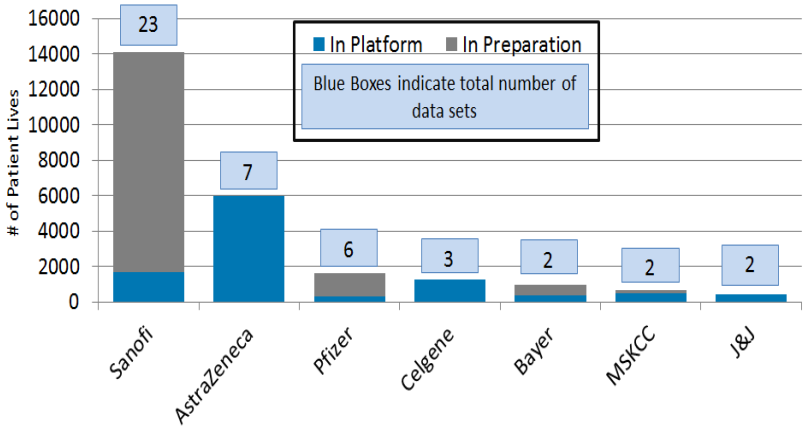




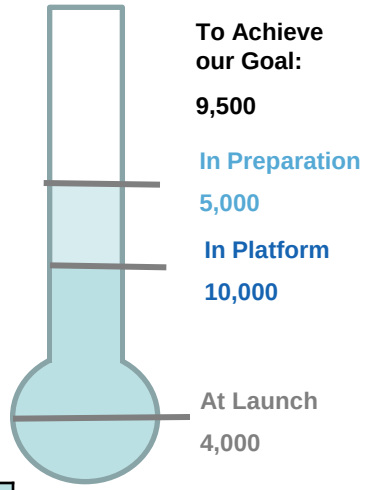


Patient Lives by Data Provider

In Platform & In Preparation



Progress to 25,000 Patient Lives Target



Key Metrics

Total Users	New Users This Month	Countries	Total Downloads
253	20	21	816

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.

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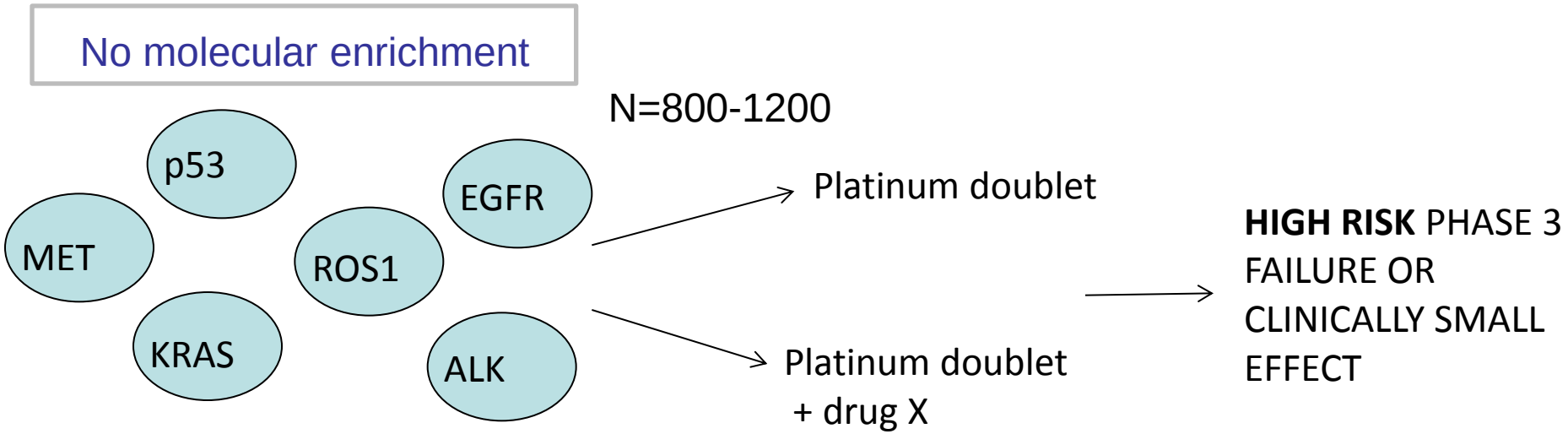
The Role of Non-Randomized Trials for the Evaluation of Oncology Drugs

Gideon Blumenthal, MD
FDA

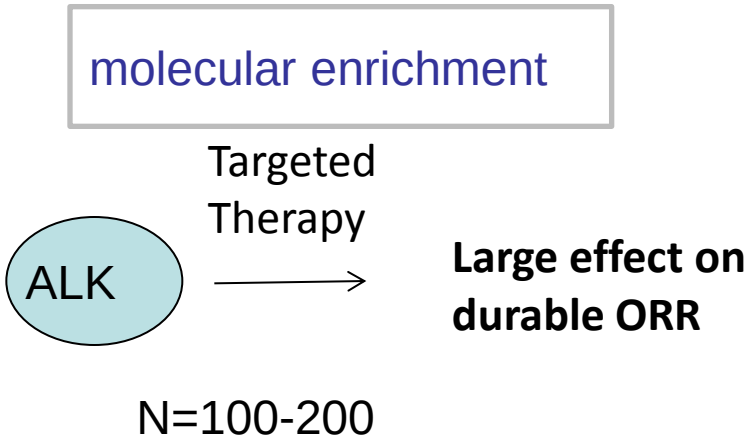
High magnitude and durable Overall Response Rates (ORR) in single arm trials in oncology

- 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"



Challenges with "new paradigm"



- 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?

Hazardous journeys

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

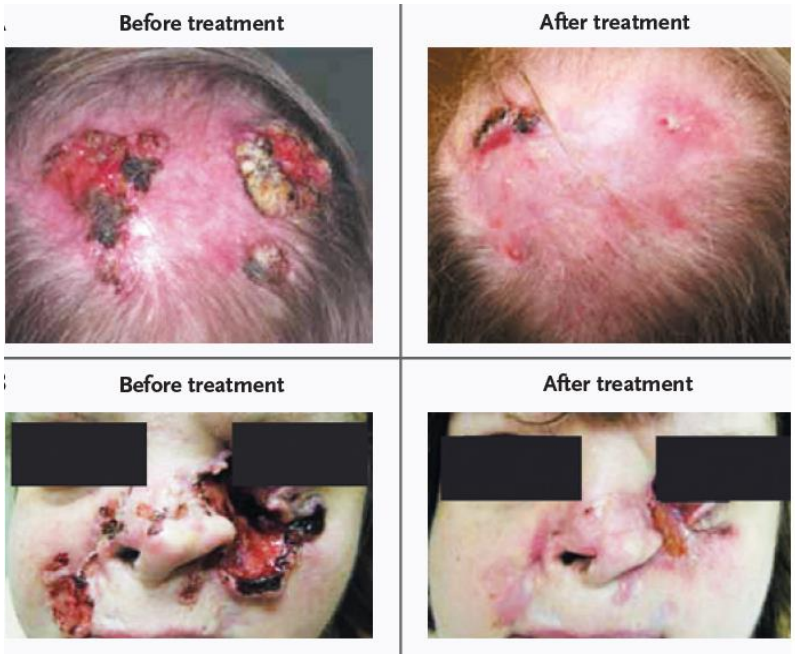
BMJ 2003; 327:1459

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

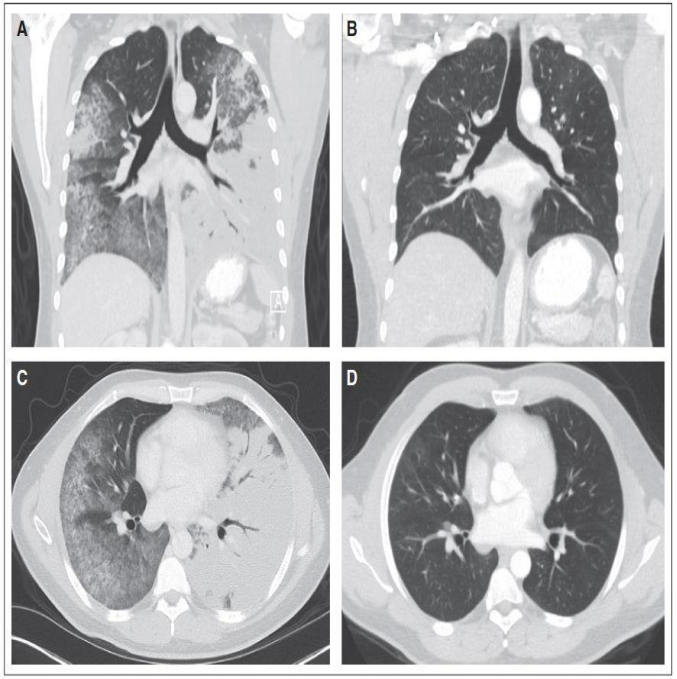
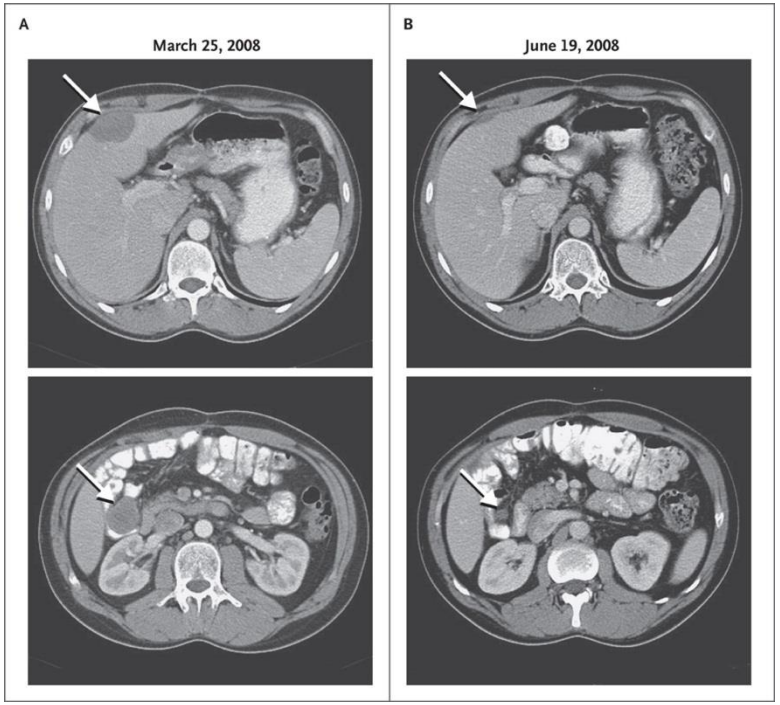


Fig 4. Response of an *ROS1*-positive patient with advanced non–small-cell lung cancer to crizotinib. Computed tomography scans of the chest were obtained (A and C) at baseline and (B and D) after 12 weeks of crizotinib. Shown are (A and B) coronal reconstructions and (C and D) axial slices.

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

Response where you need an arrow to point it out



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

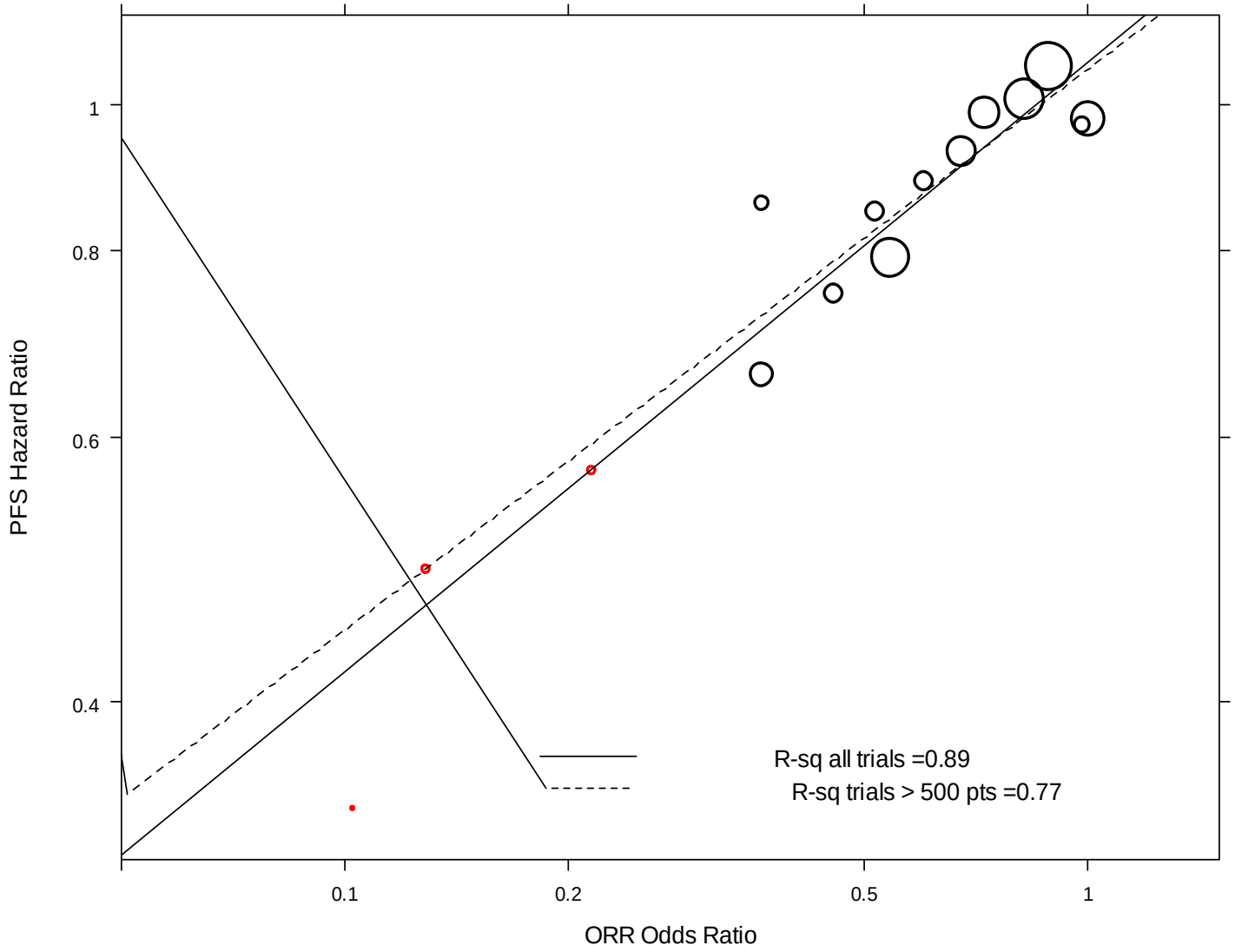
Non small cell lung cancer (NSCLC) meta- analysis

Drug	Control Arm	Design	N	Patient Population	Primary Endpoint
Crizotinib	Pem (or doc)	Head-to-Head	347	2L ALK+	PFS (IRC)
Afatinib	Cis + pem	Head-to-Head	345	1L EGFRm	PFS (IRC)
Erlotinib	Cis(car) + doc (gem)	Head-to-Head	174	1L EGFRm	PFS (INV)
Nab-pac + car	Car + pac	Head-to-Head	1052	1L	ORR (IRC)
Cetuximab	Cis + tax	Add-On	676	1L	PFS (IRC)
Cetuximab	Cis + vin	Add-On	1125	1L	OS
Vandetanib	Erl	Head-to-Head	1240	2L+	PFS (INV)
Vandetanib	Pem	Add-On	534	2L+	PFS (INV)
Vandetanib	Doc	Add-On	1391	2L+	PFS (INV)
Gefitinib	Doc	Head-to-Head	1466	2L+	OS (NI)
Bevacizumab	Cis + gem	Add-On	692	1L NSq	PFS (INV)
Bevacizumab	Cis + gem	Add-On	698	1L NSq	PFS (INV)
Pemetrexed + cis	Cis + gem	Head-to-Head	1725	1L	OS (NI)
Bevacizumab	Car + pac	Add-On	850	1L NSq	OS
Pemetrexed	Doc	Head-to-Head	571	2L	OS (NI)

Molecularly enriched

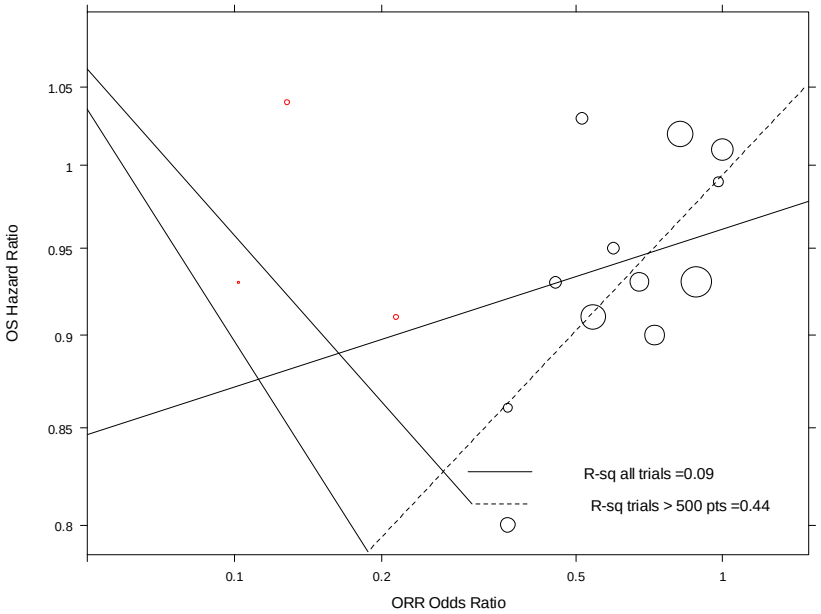
Not Molecularly enriched

Results: Trial level PFS HR versus ORR odds ratio

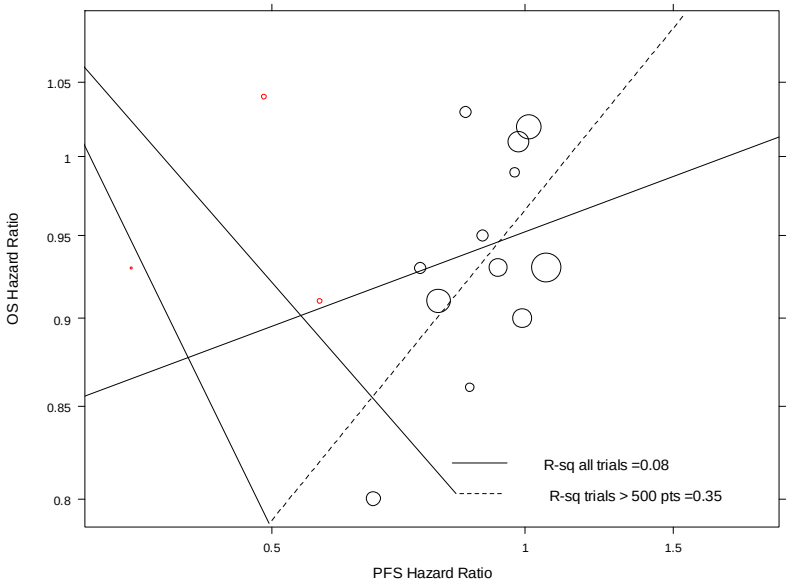


Results: trial level associations between ORR and OS and PFS and OS

ORR and OS

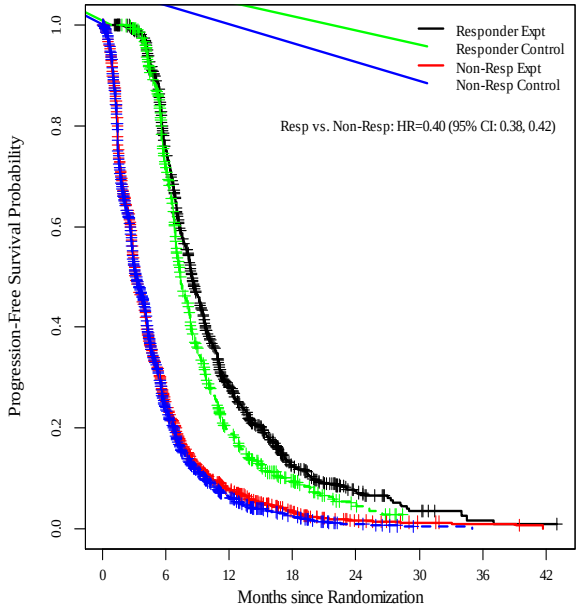


PFS and OS



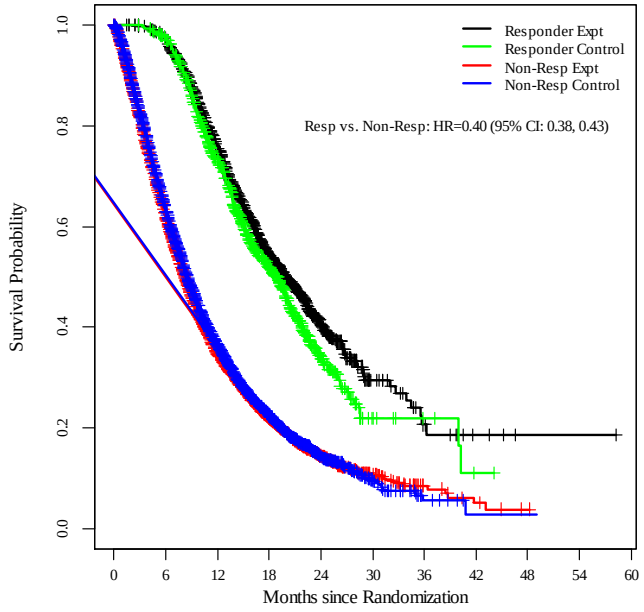
Results: patient-level responder analysis

response and PFS



Responder Expt	1682	1174	358	104	28	8	2	1
Responder Control	1012	666	141	42	10			
Non-Resp Expt	4804	1011	254	73	16	6	3	
Non-Resp Control	5069	946	203	57	11	1		

response and OS



Responder Expt	1682	1605	1129	598	188	29	11	4	1	1
Responder Control	1012	968	651	343	91	10	5	1		
Non-Resp Expt	4804	2799	1338	596	175	53	12	5	1	
Non-Resp Control	5069	3000	1474	634	189	39	7	1	1	

Conclusions

- On trial level, meta-analysis randomized, active-controlled trials submitted since 2003 indicates strong correlation (R-sq=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

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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.
  - RW Makuch & RM Simon. Sample size considerations for non-randomized comparative studies. J. Chron. Dis. 33: 175-181, 1980.
  - DO Dixon & RM Simon. Sample size considerations for studies comparing survival curves using historical controls. J. Clin. Epidemiology 41: 1209-1214, 1988.
  - PF Thall & R Simon. Incorporating historical control data in planning phase II clinical trials. Stat. in Med. 9:215-228, 1990.
  - EL Korn & B Freidlin. Conditional power calculations for clinical trials with historical controls. Stat in Med 25:2922-31, 2006.

Number of patients needed on test treatment
Control durable response rate .10
Test rx durable response probability .40

m historical controls	Pts on test rx for power 0.90	Pts on test rx for power .85 with margin .05	Pts on test rx for power .85 with margin .10
50	33	60	500
100	25	37	85

External controls for a biomarker selected population

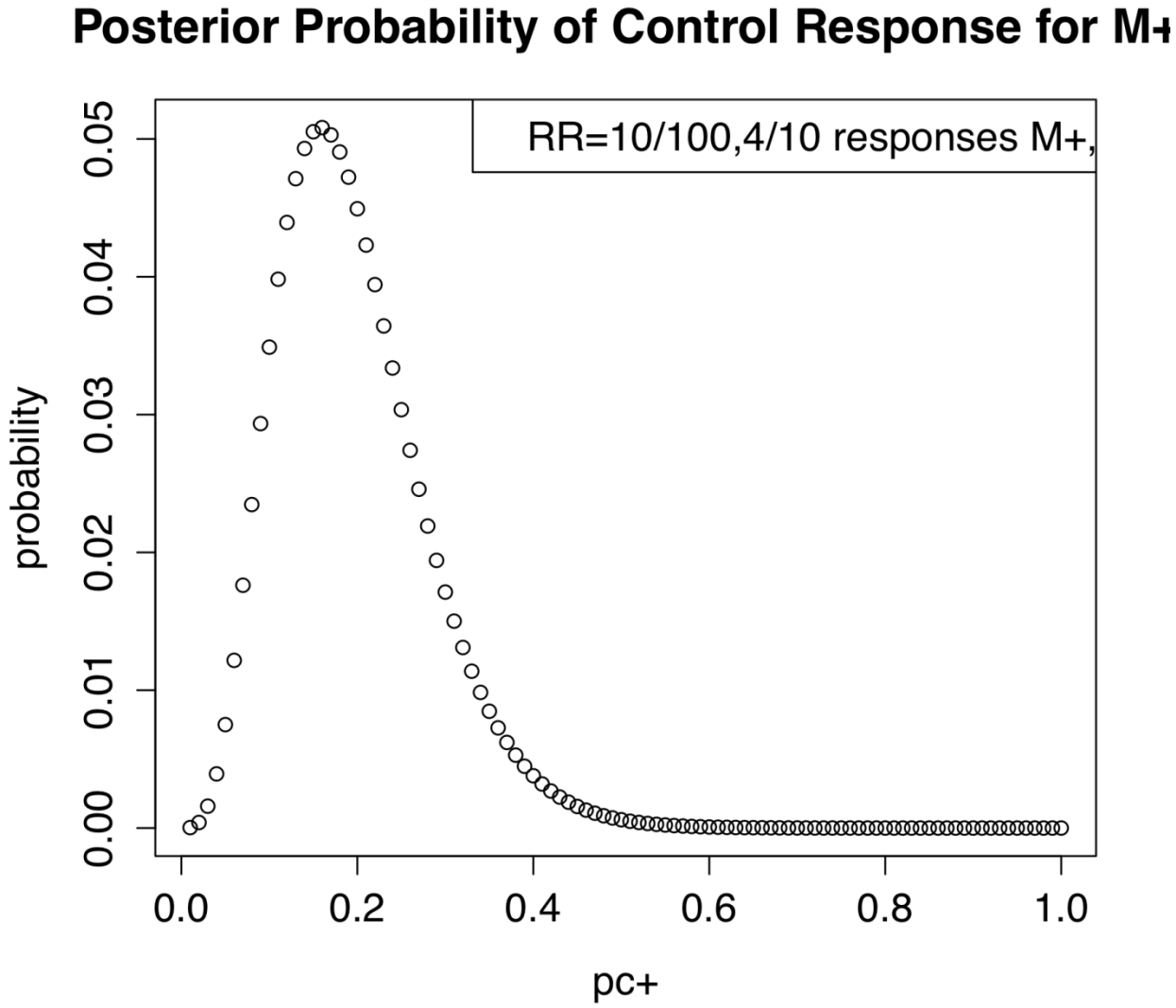
- Assay archived tumor tissue on a sample of control responders to estimate the fraction (f) of durable responders that are marker + in controls
- The overall durable response rate r in controls and the fraction f enable one to compute the posterior distribution of durable response rate for marker + 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+

$$f = \frac{prev * n * p_{C+}}{n * p_C}$$

$$\hat{p}_{C+} = \frac{f}{prev}\hat{p}_C$$

$$e.g.\ \hat{p}_{C+} = \frac{4/10}{.25}.10 = .16$$


Posterior Probability of Control Response for M+
RR=10/100,4/10 responses M+,
probability
0.00
0.01
0.02
0.03
0.04
0.05
0.0
0.2
0.4
0.6
0.8
1.0
pc+

- 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

Control RR	f	Test rx response prob	n for power .85
10/100	4/10	.45	130
20/200	8/20	.45	40
20/200	8/20	.40	75

Prevalence M+=.25

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

Josh Sommer
Chordoma Foundation

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