Basel Biometrics Society seminar
Basel, 26th June 2018

BBS Seminar:
RCTs, personalized medicine, and surrogacy
Date: Tuesday, June 26, 2018, 15:30-17.45
Venue: Auditorium Building 71, Roche Campus,
Grenzacherstrasse, Basel

Precision Medicine Needs Randomized Trials

Everardo D. Saad, MD
Louvain-la-Neuve, Belgium

IDDI
ADDING VALUE TO CLINICAL DATA

TRIAL DESIGN - RANDOMIZATION -
DATA MANAGEMENT - BIOSTATISTICS

The changing face of oncology trials

- Increasing knowledge on the biological features of cancer
- Availability of a growing number of targeted therapies*
- Changing regulatory environment

*Monoclonal antibodies, inhibitors of protein kinases, growth factors and other signaling molecules, and various forms of immunotherapy

Some recent approvals

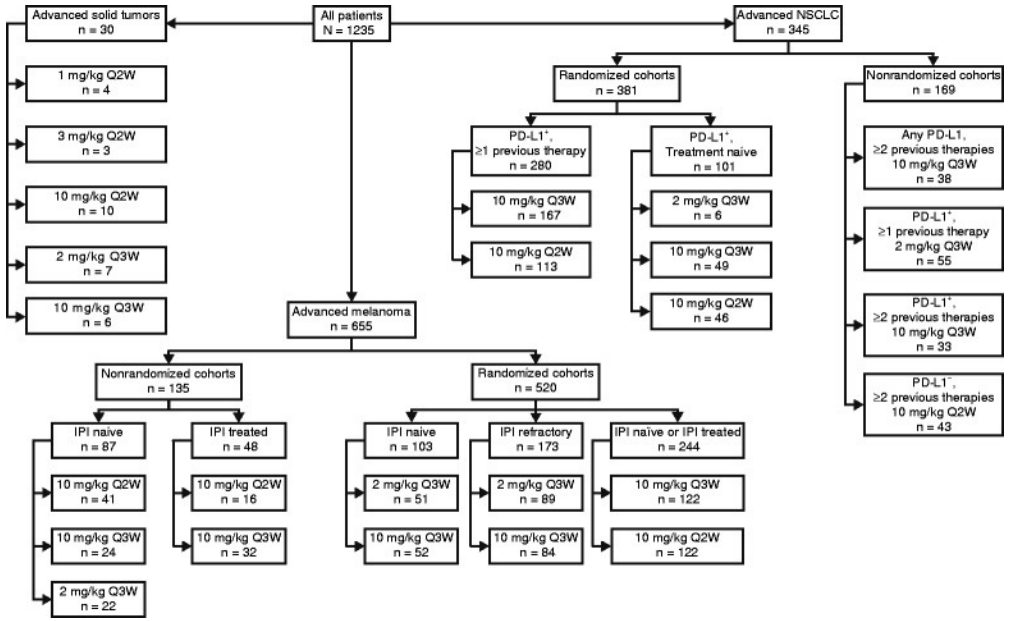
Crizotinib

Table 1. Efficacy data

	Study 1001		Study 1005	
	INV	IRC	INV	IRC
Primary endpoint	***N* = 116**	***N* = 105**	***N* = 135**	***N* = 105**
Response rate[a] (95% CI)	71 (61.2%; 52%–70%)	55 (52.4%; 42%–62%)	68 (50.0%; 42%–59%)	44 (41.9%; 32%–52%)
Complete response	2	0	1	1
Partial response	69	55	67	43
Duration of response (partial response)	48.1 wks	58.1 wks	41.9 wks	33.1 wks
Median (range)[b]	(4.1+ to 76.6+)	(7.3+ to 76.6+)	(6.1+ to 42.1+)	(6.1+ to 42.1+)

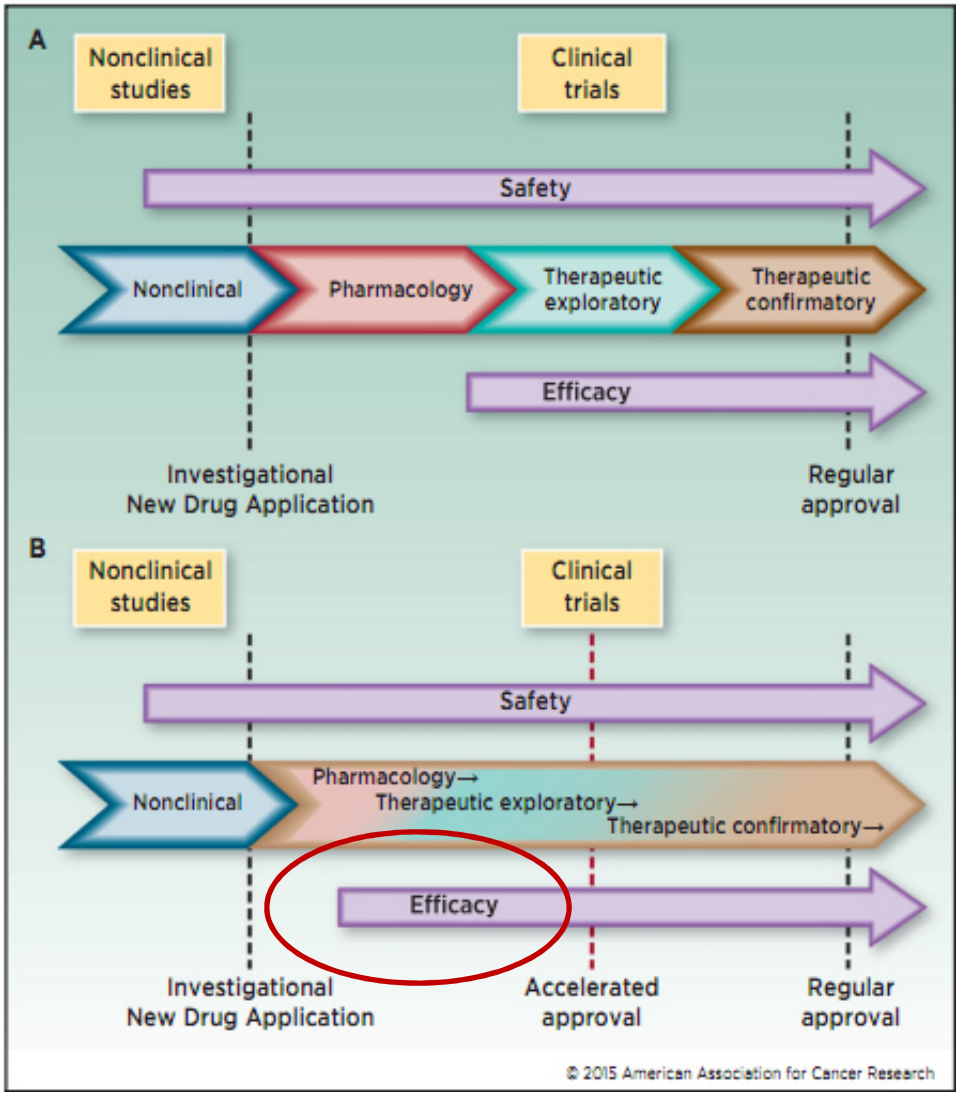
[a]RECIST v1.0 in Study 1001 and v1.1 in Study 1005.
[b]The Kaplan–Meier method with censored values (+).

Pembrolizumab



Clin Cancer Res 2014;20:2029-34
Journal for Immunotherapy of Cancer 2015; 3:36

Seamless transition



Clin Cancer Res 2015;21:4545

Basis for FDA approvals

Review of Oncology and Hematology Drug Product Approvals at the US Food and Drug Administration Between July 2005 and December 2007

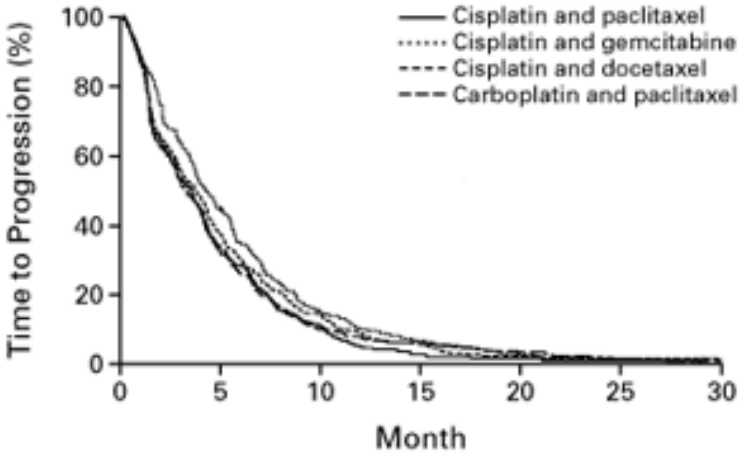
Rajeshwari Sridhara, John R. Johnson, Robert Justice, Patricia Keegan, Aloka Chakravarty, Richard Pazdur

Thirty-seven of the 53 indications were based on data from randomized studies. These randomized studies included 17 "add-on" studies in which the investigational drug plus standard chemotherapy was compared with the standard chemotherapy alone, four studies in which placebo was the comparator, and four studies in which best supportive care was the comparator (Table 1). The study sample sizes in the randomized studies ranged from 87 patients for the use of eculizumab in paroxysmal nocturnal hemoglobinuria to 19747 patients for the use of raloxifene for the reduction in risk of invasive breast cancer. The remaining 16 indications were based on data from single-arm studies with no comparison group. In these studies, the sample sizes ranged from 18 patients for the use of imatinib mesylate in dermatofibrosarcoma protuberans to 232 patients for the use of nilotinib hydrochloride monohydrate in chronic-phase chronic myeloid leukemia (Table 1). Forty-four of the 53 indications were based on results from a single study.

J Natl Cancer Inst 2010;102:230-43

Evolution

2002

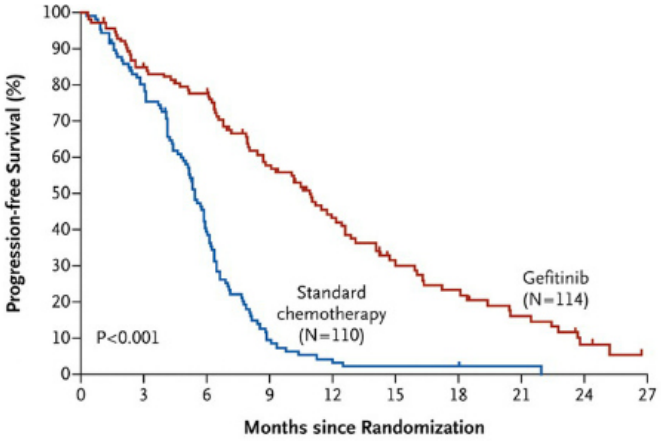


Chemotherapy

All-comers

No treatment effect

2010



Targeted therapy

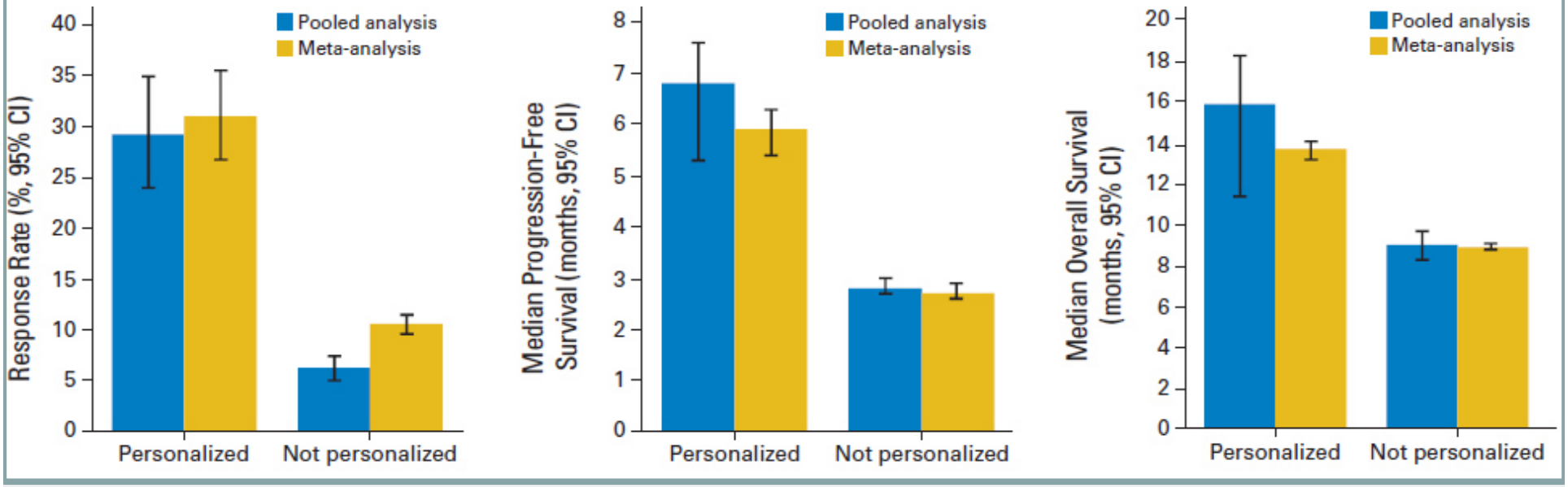
EGFR-mutated

Large treatment effect

N Engl J Med 2002;346:92; N Engl J Med 2010;362:2380

Evidence favoring precision medicine

Published phase II trials

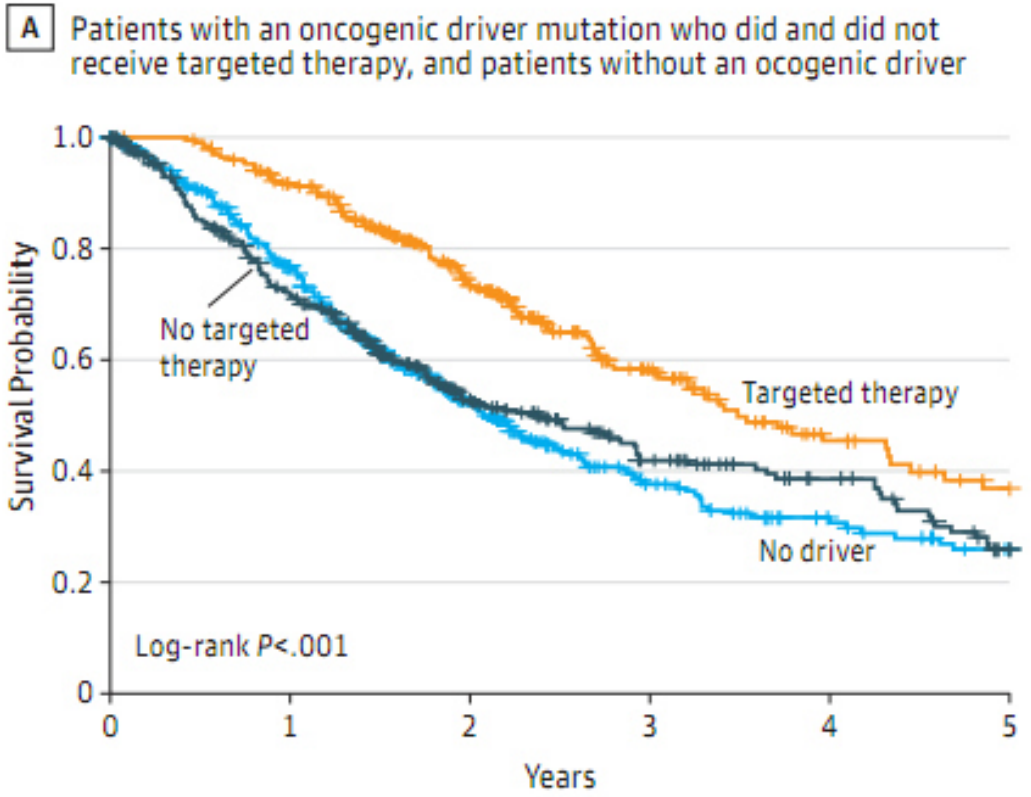


FDA-approved agents

	Relative response rate ratio		PFS		OS	
Characteristic	N	RRR (95% CI)	N	HR (95% CI)	N	HR (95% CI)
Personalized status						
Personalized	14	3.82 (2.51 to 5.82)	13	0.41 (0.33 to 0.51)	13	0.71 (0.61 to 0.83)
Non-personalized	37	2.08 (1.76 to 2.47)	38	0.59 (0.53 to 0.65)	33	0.81 (0.77 to 0.85)
P (univariate)		.009		.004		.11
P (meta-regression)*,†		.03		<.001		.07

J Clin Oncol 2015;33:3817; J Natl Cancer Inst 2015;107:djv253

Precision medicine is compelling



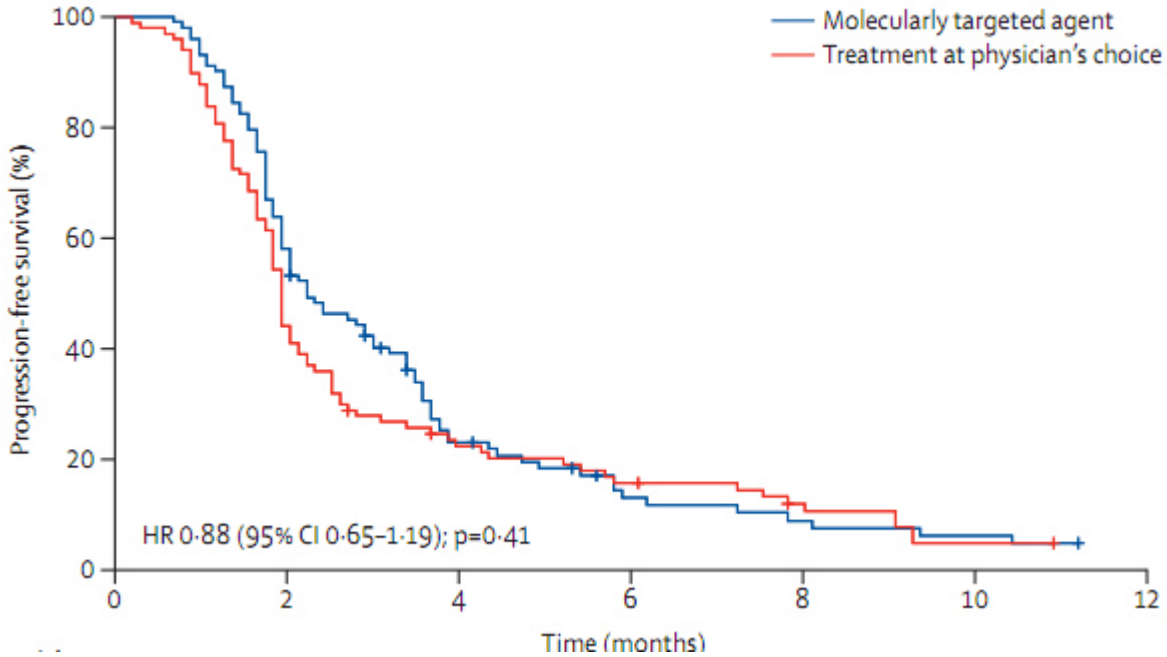
No. at risk						
Patients with oncogenic driver						
No targeted therapy	318	205	110	64	43	20
Targeted therapy	260	225	143	72	36	23
Patients with no driver	360	250	122	59	36	23

JAMA 2014;311:1998-2006

Is rationale enough?

Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial

Christophe Le Tourneau, Jean-Pierre Delord, Anthony Gonçalves, Céline Gavoille, Coraline Dubot, Nicolas Isambert, Mario Campone, Olivier Trédan, Marie-Ange Massiani, Cécile Mauborgne, Sebastien Armanet, Nicolas Servant, Ivan Bièche, Virginie Bernard, David Gentien, Pascal Jezequel, Valéry Attignon, Sandrine Boyault, Anne Vincent-Salomon, Vincent Servois, Marie-Paule Sablin, Maud Kamal, Xavier Paoletti, for the SHIVA investigators



Lancet Oncol 2015;16:1324-34

Let's not forget toxicity

Molecularly targeted therapy based on tumour molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial

Christophe Le Tourneau, Jean-Pierre Delord, Anthony Gonçalves, Céline Gavoille, Coraline Dubot, Nicolas Isambert, Mario Campone, Olivier Trédan, Marie-Ange Massiani, Cécile Mauborgne, Sebastien Armanet, Nicolas Servant, Ivan Bièche, Virginie Bernard, David Gentien, Pascal Jezequel, Valéry Attignon, Sandrine Boyault, Anne Vincent-Salomon, Vincent Servois, Marie-Paule Sablin, Maud Kamal, Xavier Paoletti, for the SHIVA investigators

	Patients who received molecularly targeted agents (n=100*)			Patients who received cytotoxic chemotherapy (n=91†)		
	Grade 2 necessitating drug interruption or delay‡	Grade 3	Grade 4	Grade 2 necessitating drug interruption or delay	Grade 3	Grade 4
Any event§	12 (12%)	36 (36%)	7 (7%)	9 (10%)	28 (31%)	4 (4%)

Lancet Oncol 2015;16:1324-34

Recent ethical concerns

Early Accelerated Approval for Highly Targeted Cancer Drugs

Bruce A. Chabner, M.D.

If patients with incurable disease who have the right biomarker for response are informed of these impressive early results, they will want and perhaps deserve access to the new drug and may not accept random assignment to a modestly effective and toxic standard agent. The phase 3 trial may lack equipoise in the eyes of both physicians and patients.

N Engl J Med 2011;364:1087-9

Historical debate (the 70's)

1972

CONTROLLED STUDIES IN CLINICAL CANCER RESEARCH

THOMAS C. CHALMERS, M.D., JEROME B. BLOCK, M.D., AND STEPHANIE LEE, M.A.

RANDOMIZE THE FIRST PATIENT!

1974

NON-RANDOMIZED CONTROLS IN CANCER CLINICAL TRIALS

EDMUND A. GEHAN, PH.D., AND EMIL J FREIREICH, M.D.

■ ■ ■

2009

The Need for Large-Scale Randomized Evidence Without Undue Emphasis on Small Trials, Meta-analyses, or Subgroup Analyses

Charles H. Hennekens, MD, DrPH

David DeMets, PhD

2014

Improving the Drug Development Process
More Not Less Randomized Trials

Benjamin Djulbegovic, MD, PhD

Iztok Hozo, PhD

John P. A. Ioannidis, MD, DSc

2016

Evaluating interventions for Ebola: The need for randomized trials

Thomas R Fleming[1] and Susan S Ellenberg[2]

The case of AZT for HIV infection

THE EFFICACY OF AZIDOTHYMIDINE (AZT) IN THE TREATMENT OF PATIENTS WITH AIDS AND AIDS-RELATED COMPLEX

A Double-Blind, Placebo-Controlled Trial

Survival

Nineteen subjects in the placebo group and 1 in the AZT group died during the study ($P<0.001$ by the Cox regression model).

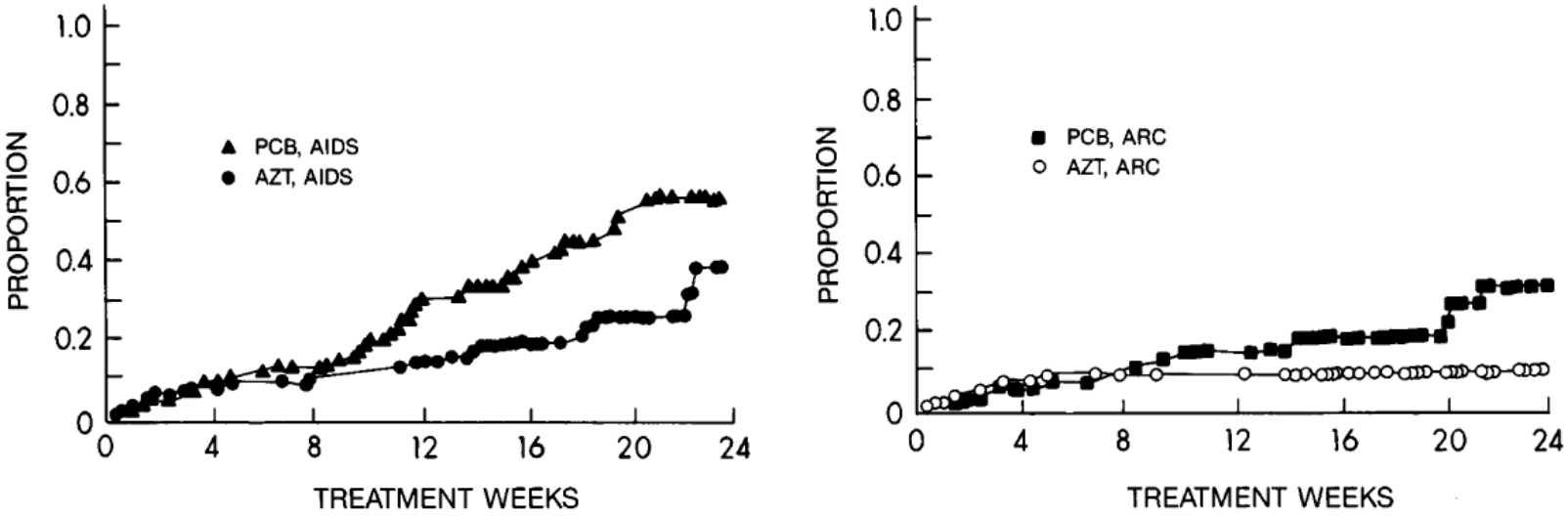


Figure 1. Proportion of Patients in Whom Opportunistic Infections Developed during the Study (Kaplan–Meier Product–Limit Method). The left panel shows infection among patients with AIDS who were receiving AZT or placebo (PCB), and the right panel shows infection among those with AIDS-related complex (ARC).

N Engl J Med 1987;317:185-91

Perils of non-randomized evidence

- Selection bias
- Unknown confounders
- Stage migration
- Temporal trends in supportive care etc.
- Different populations between early- and late-phase trials

Benefits of randomization

- Controls selection bias and the problems of historical/contemporary comparisons
- Provides an internal control for all efficacy and safety outcomes
- Allows reliable conclusions about small benefits on important clinical endpoints
- Disentangles the prognostic *vs*. predictive impact of molecular alterations
- Allows validation of predictive/surrogate biomarkers

Randomization *vs.* what?

- Experimental *vs.* standard of care (SOC)
- Experimental *vs.* treatment of physician's choice (TPC)
- SOC ± experimental
- TPC ± experimental
- Single agent *vs.* combination
- Different doses
- Different schedules
- Different durations (e.g., randomized discontinuation)
- Immediate *vs.* delayed administration

Drug/biomarker pair is the key

- Rituximab and CD20
- Trastuzumab/lapatinib and HER-2
- Imatinib/dasatinib/nilotinib and BCR-Abl/KIT
- Erlotinib/gefitinib/afatinib and EGFR activating mutations
- Osimertinib and EGFR T790M mutation
- Cetuximab/panitumumab and KRAS
- Crizotinib/ceritinib/alectinib and ALK-EML
- Vemurafenib/dabrafenib and BRAF
- Pembrolizumab and MSI-H/MMR defficiency

Validation of biomarkers

To validate a predictive biomarker

- Randomized trials are needed

Nature Rev Clin Oncol 2010;7:309

Validation of biomarkers

To validate a predictive biomarker

- Randomized trials are needed
- Randomized trials are needed on biomarker+ and biomarker- patients

Nature Rev Clin Oncol 2010;7:309

Validation of biomarkers

To validate a predictive biomarker

- Randomized trials are needed
- Randomized trials are needed on biomarker+ and biomarker- patients
- Large randomized trials are needed (because interaction tests lack power)

Nature Rev Clin Oncol 2010;7:309

Validation of biomarkers

To validate a surrogate biomarker-based endpoint (*e.g.* circulating tumor DNA),

- Randomized trials are needed
- Large randomized trials are needed
- Several randomized trials are needed (to confirm that the treatment effect on the surrogate is predictive of the treatment effect on the true endpoint)

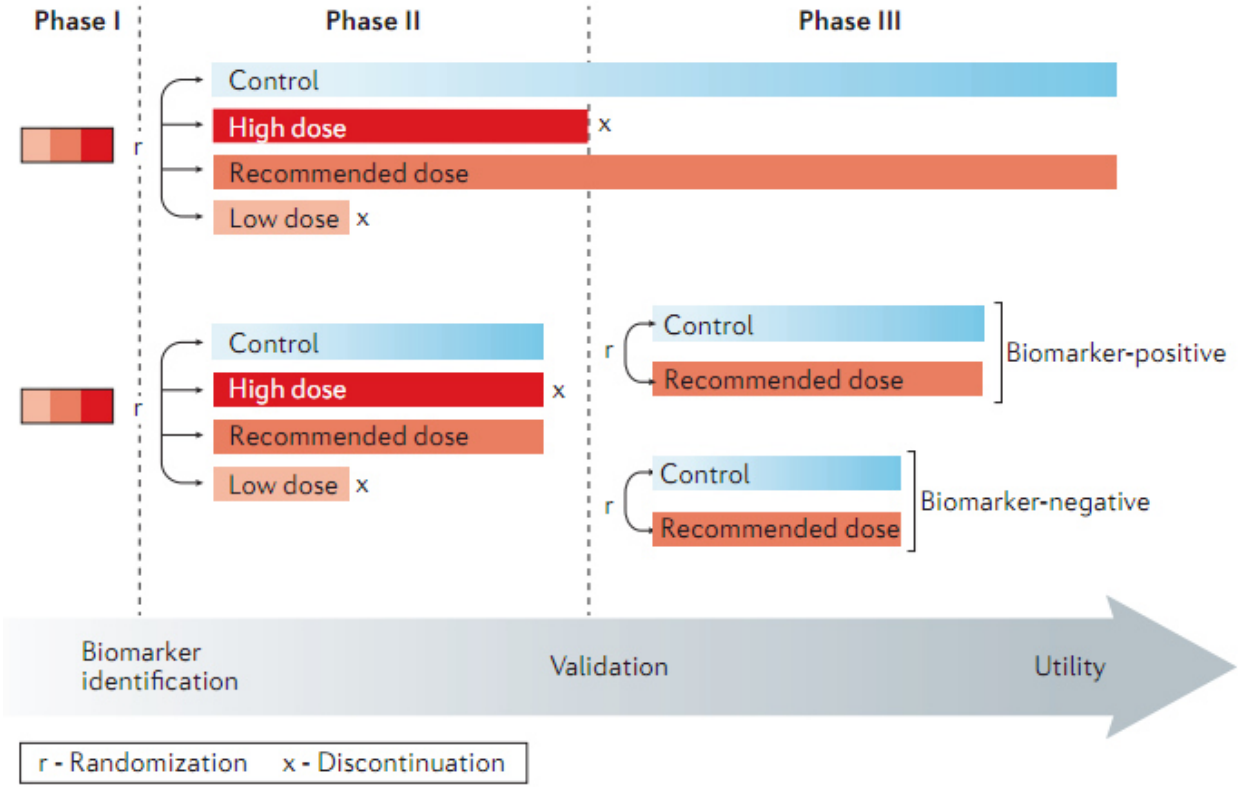
Nature Rev Clin Oncol 2010;7:309

Randomize as soon as possible

OPINION

Precision medicine needs randomized clinical trials

Everardo D. Saad, Xavier Paoletti, Tomasz Burzykowski and Marc Buyse



Nat Rev Clin Oncol 2017;14:317

When can we forgo randomization?

Role of randomized phase III trials in an era of effective targeted therapies

Manish R. Sharma and Richard L. Schilsky

Box 1 | Six criteria for targeted therapies to be approved without a phase III trial

- Preclinical studies should confirm that the drug targets a driver of the malignant phenotype
- An analytically validated assay should be available to identify which tumors have the intended target
- The drug should be studied in a population of patients that are selected on the basis of having the target
- The response rate and average response duration should indicate a clinically meaningful improvement over that which would be expected based on historical data for the existing standard of care in the same subset of selected patients
- These two outcome measures (response rate and response duration) must be interpreted in the context of the disease setting
- There should be no life-threatening safety concerns about the drug based on the total body of available data

Nat Rev Clin Oncol 2012;9:208

Randomization in phase I

- As soon as expansion cohorts kick off
- To different doses/schedules, preferably with a SOC control arm
  - If SOC not available, any treatment other than the investigational therapy (including agents of the same class)
- Early stopping for outstanding activity, based on interim analyses of biomarkers

Randomization in phase II

- To select regimens more likely to succeed in phase III
- Whenever indicated , include assessment of biomarkers
- Early stopping for outstanding efficacy, based on interim analyses of intermediate endpoints

Randomization in phase III

- Important to include a true control (best treatment patients would receive outside of trial)
- Early stopping for outstanding efficacy, based on interim analyses of surrogate endpoints