Issues in accelerated approval

David Ross, M.D., Ph.D.
Office of Oncology Drug Products
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Disclaimer

"The views expressed herein are not necessarily those of the U.S. Food and Drug Administration . . .

" . . . but they may be."

Outline

- Regular v. accelerated approval (RA v. AA)
- Oncology endpoints for RA and AA
- Issues in AA
  - Trial design
  - Confirmatory trials
  - Surrogate endpoints

Key points

- AA allows earlier access to new therapies for serious or life-threatening diseases
- AA raises complex issues in fields such as oncology that can affect the success of a development program
- Careful planning during development can minimize impact of these issues

US marketing requirements: Drugs and biologics

Under the Food, Drug, and Cosmetic Act (FDCA), a new drug or biologic may not be commercially marketed in the US unless it has been approved as safe and effective by the FDA.

- Approval is based on review of a New Drug Application (NDA) or Biologic Licensing Application (BLA)
- Application must contain acceptable scientific data including the results of tests to evaluate safety, and substantial evidence of effectiveness for the conditions for which the drug is being offered
- NDA/BLA must allow appropriate labeling

NDA/BLA standard of evidence

"…substantial evidence…"

"…evidence consisting of adequate and well controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could be fairly and responsibly concluded by such experts that the drug will have the effect it purports or is represented to have…"

What's an effect?

- Is it:
  - Clinical
  - Pharmacological
  - Psychological
- FDCA does not specify standard

Effectiveness standard

- Drugs cause clinical risks
- Benefits should be clinical as well
- Effect must be "clinically meaningful" (Warner-Lambert v. Heckler, 1986)
- Evidence must come from "adequate and well-controlled trials" (21 CFR 314.126)
- Substantiation of results required
  - Two trials frequently needed for approval
  - FDAMA (1997) allows FDA to approve on basis of one trial

Regular approval (RA) standard

- Measurable effects on
  - survival
  - irreversible morbidity
  - pharmacologic surrogate endpoint
    - well validated (e.g., HTN)
    - well understood disease pathophysiology
    - well understood mechanism of action
- Adequate risk characterization
- Acceptable benefit/risk ratio

RA pros and cons

- Advantages
  - Definitive evidence of benefit
  - Clear standard
- Disadvantages
  - Long timeframe for studies
  - Large sample sizes
  - High cost

“Most of the public are generally healthy and require medicines for temporary and benign illnesses such as the common cold. They usually do not want to be exposed to risks. They want the FDA to ensure their treatments will be near to absolutely safe and reasonably effective.

“The second segment of FDA's constituency is people with serious or chronic diseases such as rare diseases and cancer. These individuals want new treatments as quickly as possible and are often willing to bear substantial risks in exchange for possible efficacy. For example, cancer drugs are often known to be very toxic, but a person who may lose his or her life to cancer is usually willing to take highly toxic chemotherapy drugs and suffer horrendous side effects in exchange for a hope of recovery.”

Meyers AS. Testimony before Senate HELP committee, 1 March 2005

Accelerated approval (AA)

- Response to HIV epidemic
- Intended to provide earlier access to therapies for serious diseases
- Final rule published in 1992
- Codified in 21 CFR 314.500 and 601.40
- Guidance for Industry – Fast Track Drug Development Programs: Sep 1998

AA scope

- Applies to drugs and biologics for serious or life-threatening illnesses "that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy).”

AA requirements

Marketing approval may be based on

- Non-traditional efficacy measure
  - a demonstrated effect on a surrogate endpoint that is reasonably likely to predict clinical benefit
  - an effect on a clinical endpoint other than survival or irreversible morbidity
  - NOT: Borderline evidence regarding a clinical benefit endpoint
- Adequate risk characterization
- Acceptable benefit/risk ratio

AA post-marketing requirements

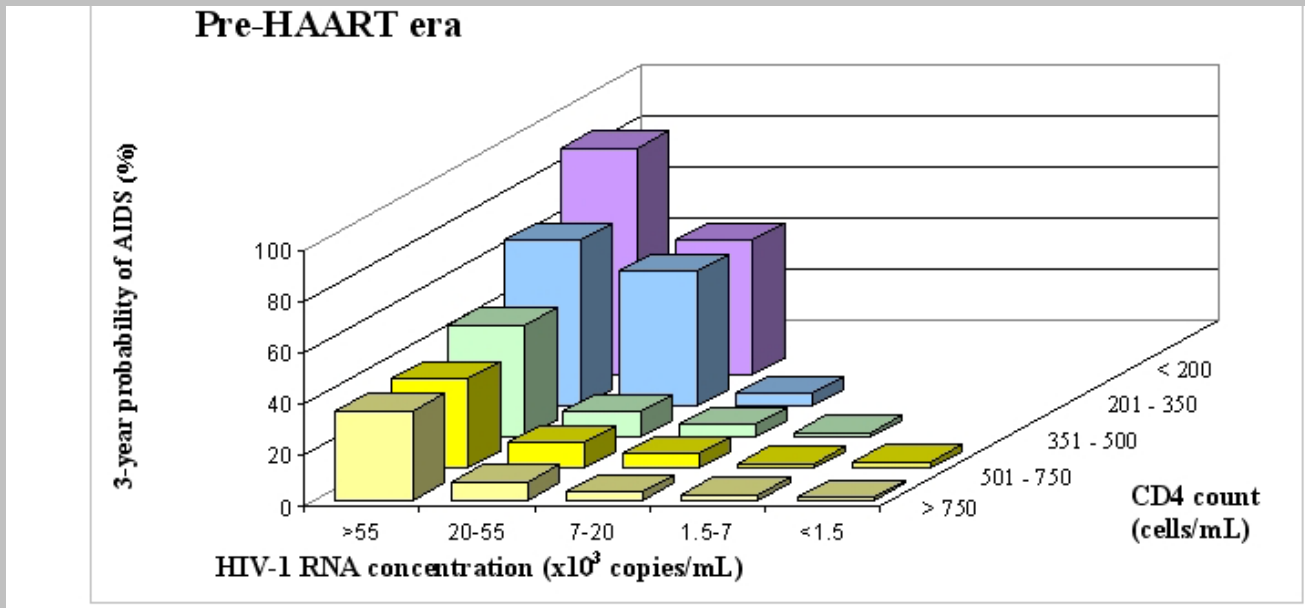
- Applicant must verify and describe benefit via confirmatory trial (CT)
- CT usually underway at time of AA
- CT must be conducted with due diligence
- Potential post-marketing restrictions on distribution and promotion

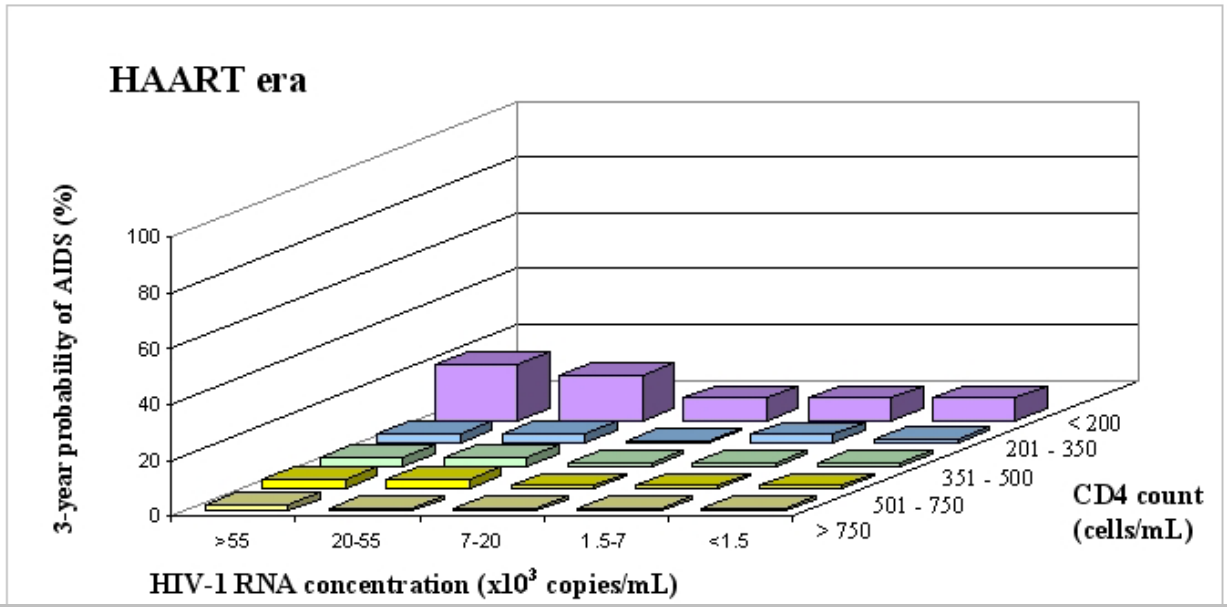
AA withdrawal

- Conditions
  - Post-marketing study fails to verify benefit
  - applicant fails to perform required study with due diligence
  - Post-marketing restrictions inadequate to assure safe use
  - failure to adhere to post-marketing restrictions
  - promotional materials false/misleading
- Requires a Part 15 hearing

Example: AA in HIV/AIDS

- Change in paradigm
  - Improved understanding of HIV infection and AIDS pathophysiology
  - sensitive and reproducible viral assays
  - combination anti-viral therapy
- Clinical endpoints no longer necessary or feasible
- Treatment-induced ↓ in plasma RNA highly predictive of meaningful clinical benefit
  - basis for either regular approval or AA
  - short term ↓ in viral load basis for AA



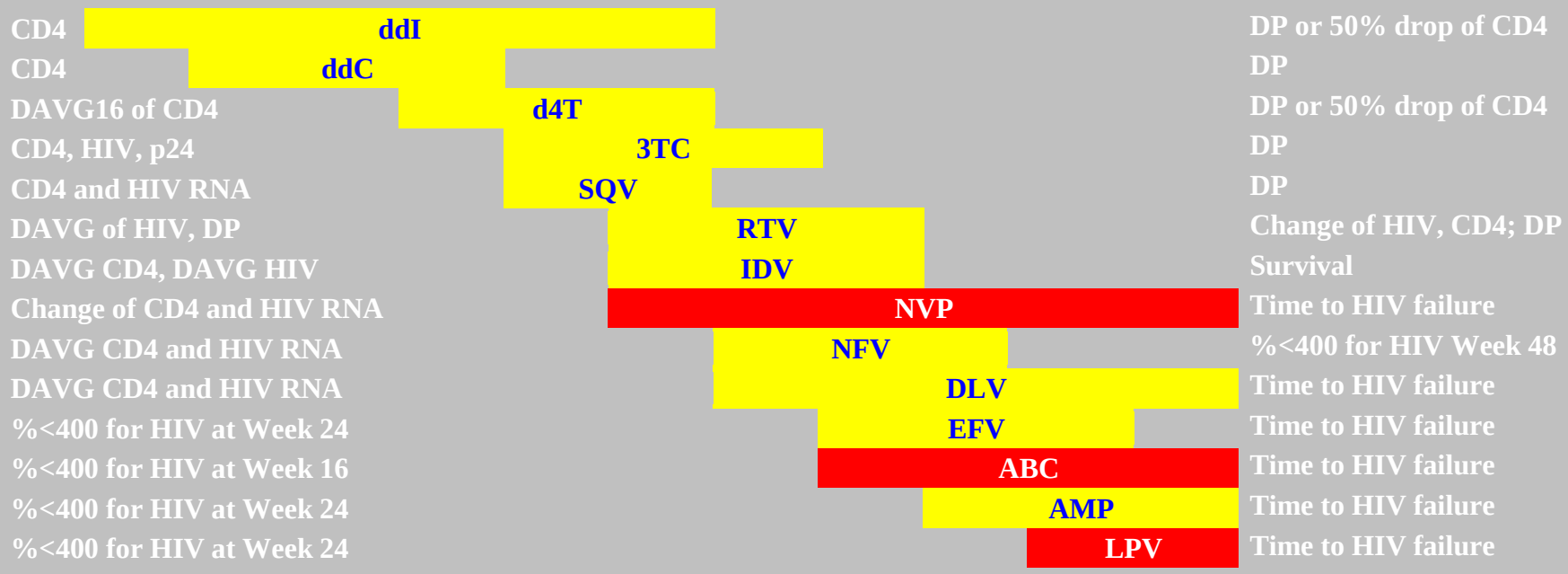


Egger M *et al.* Lancet 2002; 360:119

AA trials: the HIV paradigm

- Two large randomized trials for AA
- HIV-RNA at 24 weeks (surrogate)
- HIV-RNA in same population, same study at 48 weeks (confirmatory evidence of clinical benefit)

HIV/AIDS: AA to RA – Time and Endpoints



Development issues in oncology – I

- Investigational nature of discipline--cancer centers, cooperative groups, NCI
- Wide variety of products used by oncologists--chemotherapy, biologics, devices, supportive care, diagnostics
- Multidisciplinary approaches
- Represents >100 diseases/indications

Development issues in oncology – II

- Life-threatening nature of diseases
- Potential for distant recurrences
- Drugs have multiple MOAs; used in combination
- Risk/benefit ratio--different perspective on serious adverse events; highly trained specialists using drugs rather than GP
- Off-label uses may be standard of care
- New technologies/concepts piloted in oncology

Risks in developing oncology drugs

- Indication--lack of predictive models
- “Creative Indications”--progressively more refractory patient, market share
- Two trials versus one trial
- Dose ranging studies moving away from maximum tolerated dose (MTD) to optimum biologic dose (OBD)

Oncology trial concerns

- Minimize bias
  - Marginal activity vs. high toxicity
  - Blinding trials (difficult – combination tx)
  - Endpoints that minimize bias
  - Internal consistency of subgroups, endpoints
- Magnitude of change of endpoint
  - Clinical significance
  - Underpowered trials--guessing treatment effect
- Isolating effect of drug
- Characterizing toxicities

Oncology endpoints

- Overall survival
- Endpoints based on tumor assessment
  - Disease-free survival (DFS)
  - Response Rate (RR)
  - Progression-free survival (PFS)
  - Time to progression (TTP)
  - Time to symptomatic progression
  - Time to failure
- Endpoints based on system assessment
  - Assessment of tumor-specific symptoms
  - Specific quality of life (QOL) instruments

FDA Guidances

Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biologic Products

http://www.fda.gov/cder/guidance/1397fnl.pdf

Draft Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics

http://www.fda.gov/cder/guidance/6592dft.pdf

- Discusses historical precedents
  - Overall survival and use of tumor responses
- Issues related to endpoints based on tumor measurements (DFS, PFS, TTP, TTF)
- Endpoints based on symptom relief
- Use of biomarkers (CA-125 and PSA) as composite endpoints
- Discusses inter-relationship of endpoint selection and clinical trial designs

Overall survival (OS)

- Time from randomization to death
- Regulatory standard
  - Regular approval
  - Any setting
- Assessment
  - RCTs needed
  - Blinding not essential
- Pros
  - Clinical benefit
  - Universally accepted
  - Easily and precisely measured
- Cons
  - Requires large sample size and long follow-up
  - Cross-over therapy may “wash out” a survival effect
  - Does not capture symptomatic benefit
  - Includes noncancer deaths

Disease-free survival (DFS)

- Time from randomization to tumor recurrence or death
- Regulatory standard
  - Regular approval; AA
  - Adjuvant setting
- Assessment
  - RCTs needed
  - Blinding preferred
- Pros
  - Clinical benefit in some settings
  - Smaller sample sizes and shorter studies than OS
- Cons
  - Not validated survival surrogate
  - Susceptible to ascertainment bias
  - Differing definitions

Objective response rate (ORR)

- Proportion of patients with predefined tumor shrinkage for predefined minimum of time
- Regulatory standard
  - Regular approval (refractory lung CA); AA
  - Any setting
- Assessment
  - Can be assessed in single-arm trials (SATs) or RCTs
  - Blinding preferred in RCTs
- Pros
  - Can be assessed in SATs
  - Reflects anti-tumor acitivity
- Cons
  - Differing defintions
  - Not a direct measure of clinical benefit
  - Responses seen in a minority of patients
  - Complex assessment compared to OS
    - Number of CRs *vs* PRs?
    - Duration of responses?
    - Location of responses (e.g., liver *vs* skin)?
    - Association with symptom improvement?
    - Extent or bulk of metastatic disease?

Complete response (CR) rate

- Proportion of patients without clinically detectable CA
- Regulatory standard
  - Regular approval (e.g., acute leukemias); AA
- Assessment
  - SATs or RCTs
  - Blinding preferred in comparative studies
- Pros
  - Durable CRs represent clinical benefit in some settings
  - Can be measured in SATs
- Cons
  - Few drugs give high CR rates
  - Complex assessment compared to OS

Progression-free survival (PFS)

- Time from randomization to objective tumor progression or death
- Regulatory standard
  - Regular approval or AA (preferred endpoint in metastatic disease)
  - Any setting
- Assessment
  - RCTs needed
  - Blinding preferred
  - Blinded review recommended
- Pros
  - Activity measured in responding and stable tumors
  - Usually assessed prior to change in therapy
  - Less missing data than for symptom endpoints
  - Smaller sample sizes and shorter studies than OS
- Cons
  - Differing definitions
  - Not a direct measure of benefit
  - Not a validated OS surrogate
  - Not precisely measured
  - Subject to ascertainment bias
  - Frequent imaging studies needed
  - Extremely complex assessment compared to OS

Time to progression (TTP)

- Time from randomization to objective tumor progression
- Regulatory standard
  - Regular approval or AA
  - Second-line setting
- Assessment
  - RCTs needed
  - Blinding preferred
- Pros
  - Measured in all patients
  - Measures cytostatic activity
  - Progression is often the basis for change in therapy
  - Assessed before crossover
  - Requires smaller studies and shorter follow-up
  - Differences not obscured by cross-over effect
  - Potential for “time to symptomatic progression” endpoint
- Cons
  - Differing definitions of progression
  - Indirect measure of patient benefit.
  - Unclear clinical meaning and reliability of small TTP difference
  - Expensive to measure carefully
  - Potential for ascertainment bias

Symptom endpoints

- Regulatory standard
  - Regular approval
  - Any setting
- Assessment
  - RCTs usually needed (unless large effect)
  - Blinding preferred
- Pros
  - Clinical benefit
- Cons
  - Blinding may be difficult
  - Missing data are common
  - Few validated instruments
  - Extremely complex assessment compared to OS

Potential palliative endpoint: Health-related quality of life

- Regulatory standard
  - Regular approval
  - Second-line setting
- Assessment
  - RCTs usually needed
  - Blinding essential
- Pro: Patient's perspective on treatment
- Cons
  - Blinding is essential, but difficult to do
  - Pre-specified hypothesis essential
  - Careful serial assessments
    - Simple instruments preferred
    - Missing data makes interpretation problematic
    - Multiple endpoints and comparisons to baseline must be adjusted for in the statistical analysis plan
  - Clinical significance of score changes may be unclear
  - Is additional information gained, compared to a careful recording of toxicity/symptom data?

Treatment settings and endpoints

- Neoadjuvant
- Adjuvant
- First-line therapy
- Second-line and subsequent therapy

Lung cancer

ODAC- Dec. 16, 2003

- Focused on PFS as established vs. likely surrogate for survival
- DFS
  - Felt to be represent clinical benefit in adjuvant setting
  - Not “established” SE for locally advanced NSCLC
  - Not “established” SE for metastatic disease
- PFS felt to be “likely to predict benefit”

Colorectal cancer

ODAC- May 4, 2004

- **Data on 3 year DFS in adjuvant setting sufficient for regular approval but 5 year OS data should be reported**
- **3 yr PFS should be considered as clinical benefit in adjuvant therapy of rectal cancer**
- **PFS in metastatic setting acceptable if enough data to exclude (large) adverse impact on overall survival**

Oncology drug approval endpoints

- Regular
  - Clinical benefit
    - Overall survival
    - Improvement in tumor-related symptoms
    - DFS (selected settings)
    - PFS
  - Established surrogates
    - CR in some settings (e.g., acute leukemia)
    - PR in some settings (e.g., hormonal treatment of breast cancer)
- Accelerated
  - Time to progression
  - Response rate (RR) (most settings)

Oncology drug approvals 1990 - 2002

- 71 approvals – 57 RA, 14 AA
- 73% - endpoints other than survival
- Response rates -
  - 26/57 regular
  - 12/14 accelerated
- Trial designs
  - 47 randomized control trials (RCTs)
  - 24 single-arm trials (SATs)

Johnson J *et al.* J Clin Oncol 2003; 31:1404-1411

Oncology drug RAs 1990 – 2002

- Approvals not based on survival:
  - 73% (48/66) of all approvals
  - 67% (37/55) of all RAs
- Trial designs
  - 41 RCTs
  - 14 SATs

Summary of DDOP RA endpoints 1990 – 2002

Total	**55**	
Survival	18	
RR	26	
RR alone		10
RR+ ↓ Tumor Specific Symptoms		9
RR+ TTP		7
↓ Tumor Specific Symptoms	4	
DFS	2	
TTP	1	
Recurrent Malignant Pleural Effusion	2	
Occurrence Breast Cancer	2	
↓ impairment of creatinine clearance	1	
↓ xerostomia	1	

Johnson J *et al.* J Clin Oncol 2003; 31:1404-1411

Examples of traditional approval endpoints in oncology

- Idarubicin – Prolonged remission in leukemia
- Zinecard – Protection from cardiac toxicity
- Photofrin – Dysphagia scale
- Aredia – Skeletal morbidity scale
- Daunozome – Visible lesions of KS
- Novantrone – Pain

Oncology accelerated approvals - 2005

- 29 indications (25 different drugs)
- 13 no further confirmatory data expected
  - 10 confirmation of benefit
  - 2 restricted distribution
  - 1 indication withdrawn
- 16 indications without confirmation of CB
  - 6 approved before 2002
  - 10 approved after 2002

Trial designs and endpoints

- No concurrent comparator (SATs)
  - 19 indications
  - Endpoints: ORR, CR rate, medical castration
- Concurrent comparator (RCTs)
  - 10 indications
  - Endpoints: cytologic response, number of polyps, ORR, TTP, PFS, DFS, left ventricular function, congestive heart failure

Confirmation of clinical benefit

- docetaxel
- irinotecan
- dexrazoxane
- capecitabine
- liposomal doxorubicin
  - ovarian
- temozolomide
- imatinib mesylate
  - CML
- oxaliplatin
- anastrozole
- bortezomib

Approvals prior to 2002 without confirmation of CB

- liposomal doxorubicin (Doxil)
  - Kaposi's Sarcoma
- denileukin diftitox (ONTAK)
- liposomal cytarabine (DepoCyt)
- celecoxib (Celebrex)
- gemtuzumab ozogamycin (Mylotarg)
- alemtuzumab (Campath)
- amifostine (Ethyol)*

*Indication withdrawn by sponsor

Accelerated approval issues

- Relative merits of different trial designs
  - single arm in refractory populations
  - randomized trials in less refractory patients
- The approach of studying slightly different populations in the confirmatory setting than the AA population
- The importance of confirmatory trials being underway at the time of AA
- Difficulties identifying a reasonable surrogate endpoint
  - Rare diseases, ideal if natural history data available
  - Confirmatory trial might fail to show benefit
- Confirmatory trials may result in unacceptable risk/benefit

SATs and AA

- Pros
  - SATs require few patients
- Cons
  - SATs for AA limit study to refractory disease
  - SAT have limited ability to evaluate valuable endpoints such as TTP, QOL, and OS
  - Clinical benefit demonstrated in earlier stage. Demonstration of clinical benefit not in the approval indication
  - Difficulty in characterizing toxicities in single arm trial
  - Recommend randomized trials against “best supportive care” or chemotherapy of choice

RCTs and AA

- Pros
  - Allows AA at any disease stage
    (surrogate beats available therapy)
  - Allows "add-on" design
    (A vs A + B)
  - Allows a variety of endpoints
    - Time to event (TTP, survival)
    - Endpoints requiring blinding (symptoms, QOL)
  - Defines individual drug contribution
    - (oxaliplatin vs 5FU/LCV versus oxaliplatin + 5FU/LCV)
- Cons
  - More patients and time

Study population

- Refractory setting: unique mechanism?
- Confirmatory trials in a less refractory population than initial accelerated approval
  - Moves the drug to first-line and adjuvant trials
  - Assists in accrual after accelerated approval
  - Clinical benefit in approved indication?

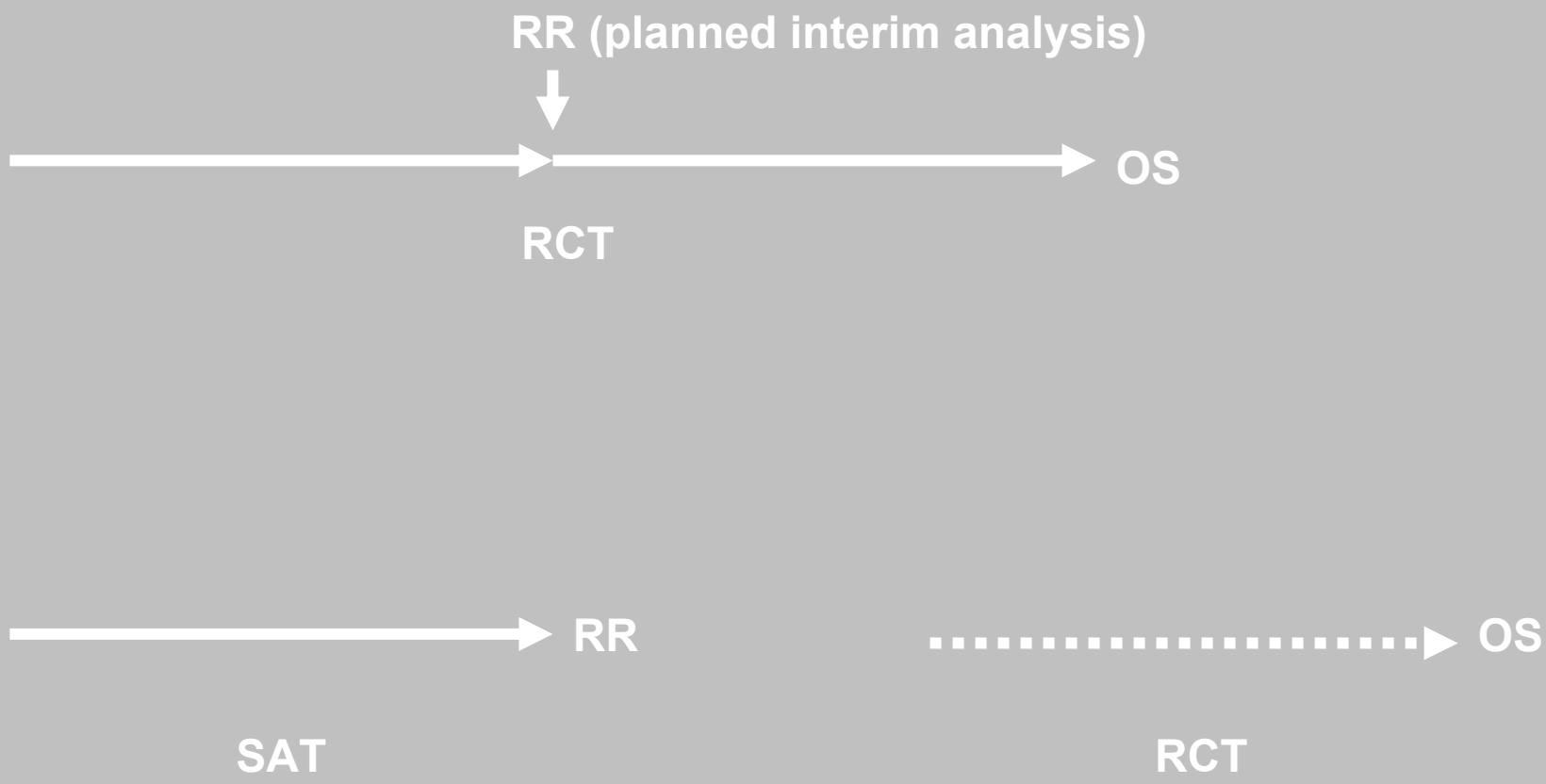
Refractory patient population

- May miss potentially active drug
- Progressively more refractory indications
- Difficulty in characterizing toxic effects

Confirmatory trials (CTs)

- "Post-marketing studies would usually be studies already underway." 21 CFR 314.510
- Confirmatory trials *integrated* in a comprehensive development program
- Choice of AA trial design may affect timing of confirmatory trials
  - Ideally, CT is continuation of AA trial (e.g., HIV, MS)
  - Depending on endpoint, oncology drug may require new trial

Timing of CTs



Planning of CTs

- Accelerated approval may impact accrual to confirmatory trials
- Early design and integration allows further questions to be formulated and answered in confirmatory trials
- Discussions prior to initiation and during the trial
  - to ensure adequate accrual
  - to discuss alternative design
- Special protocol assessments
- Clear understanding of “due diligence” with periodic review of timeline

Completion of CTs

- "FDA may withdraw approval . . . if the applicant fails to perform the required post-marketing study with due diligence . . . " (21 CFR 314.530)
- FDA Oncology Drugs AC: March 2003
  - Of 12 AA issued between 1995 and 2000, 8 were unresolved
  - Mean time from AA to completion of CT estimated to be 10 y
  - In one CT, sponsor enrolled 8 pts/year
  - 3 CTs showed minimal evidence of benefit
- CT issues
  - Enrollment difficulties – need to plan ahead
  - Loss of sense of urgency by sponsor
  - Need for a clear plan if CT does not show benefit

Use of surrogate endpoints

Treatment effects on surrogate endpoints

e.g.: ~ Tumor burden outcomes: TTP, ORR

~ Biomarkers: CEA

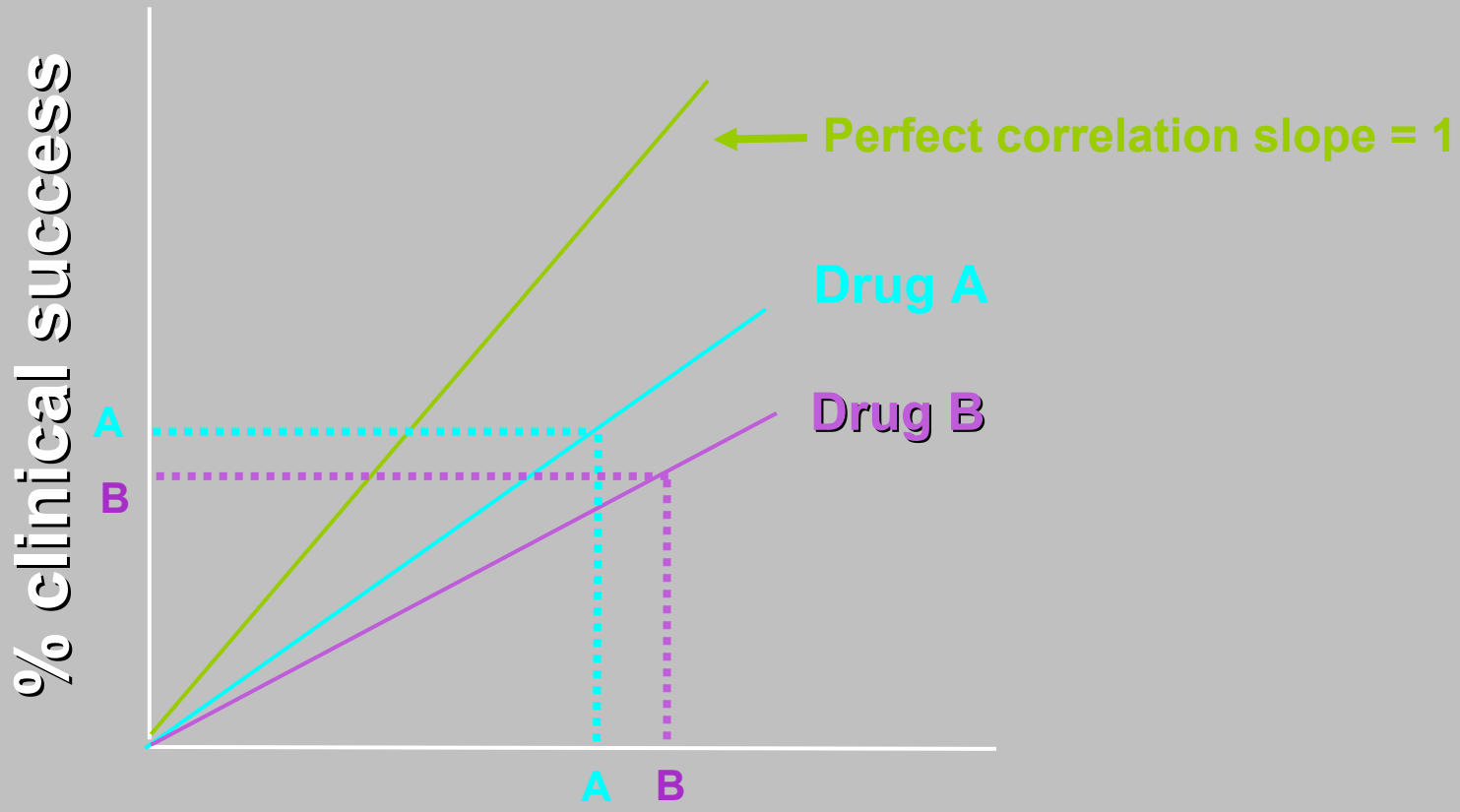
- Establishes biological activity
- But not necessarily clinical efficacy

Prentice's sufficient conditions

1. The surrogate endpoint
   must be correlated with
   the clinical outcome.

2. The surrogate endpoint
   must fully capture
   the net effect of treatment
   on the clinical outcome.

Capturing treatment effect



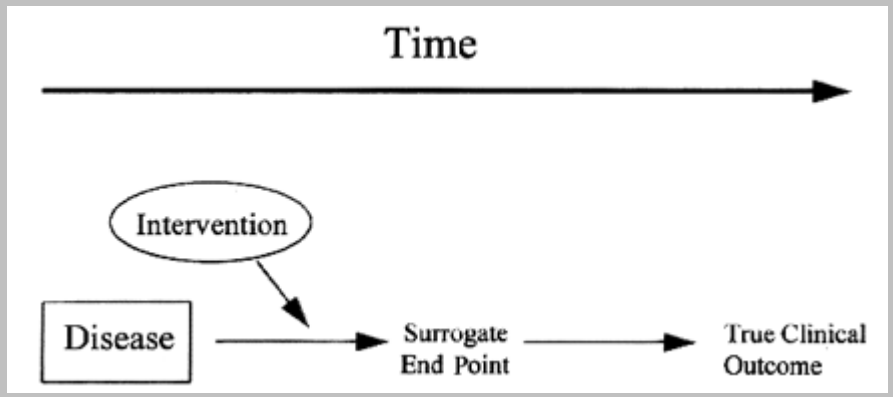
- Surrogate must measure effects similarly for all drugs studied

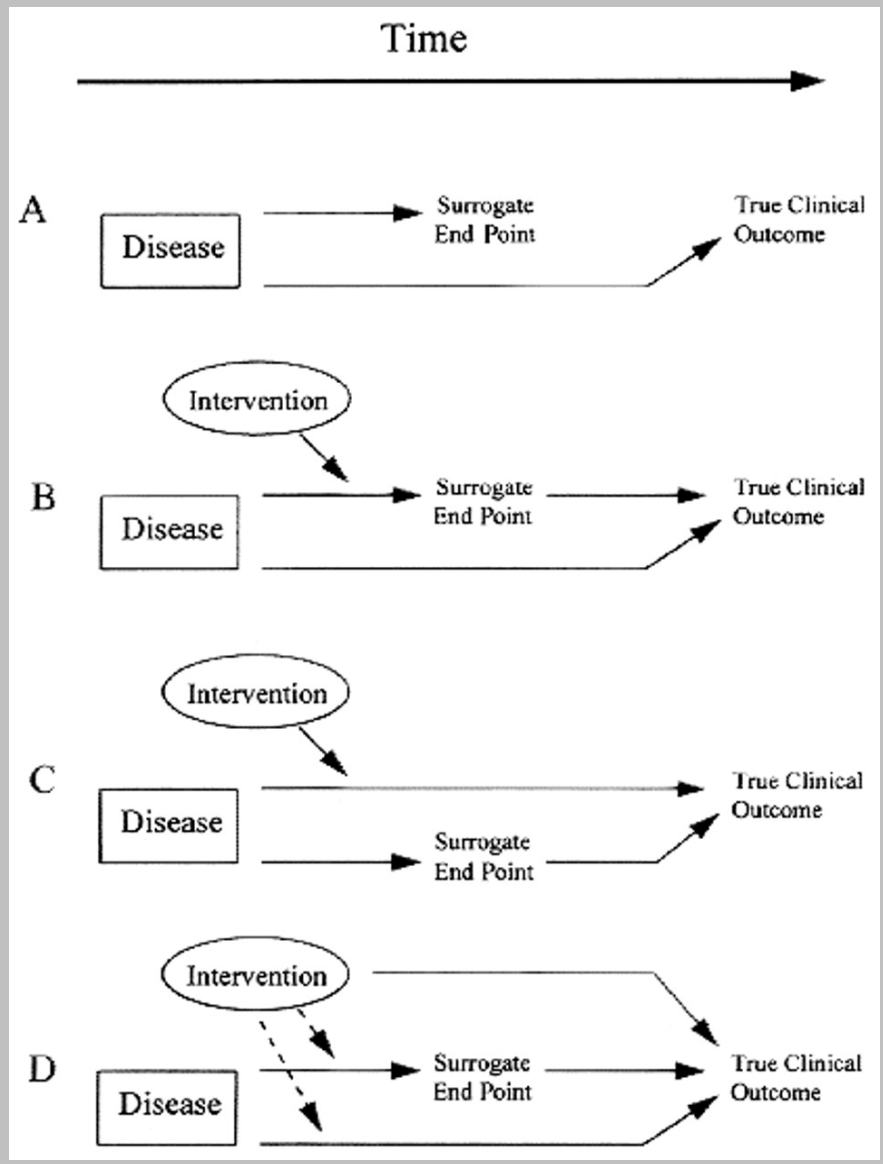
Clarithromycin for *M. avium* bacteremia

	500 mg bid	1000 mg bid	2000 mg bid
cfu/mL (2 wks)	145	34	25
mortality (12 wks)	5.7%	25.5%	28.0%

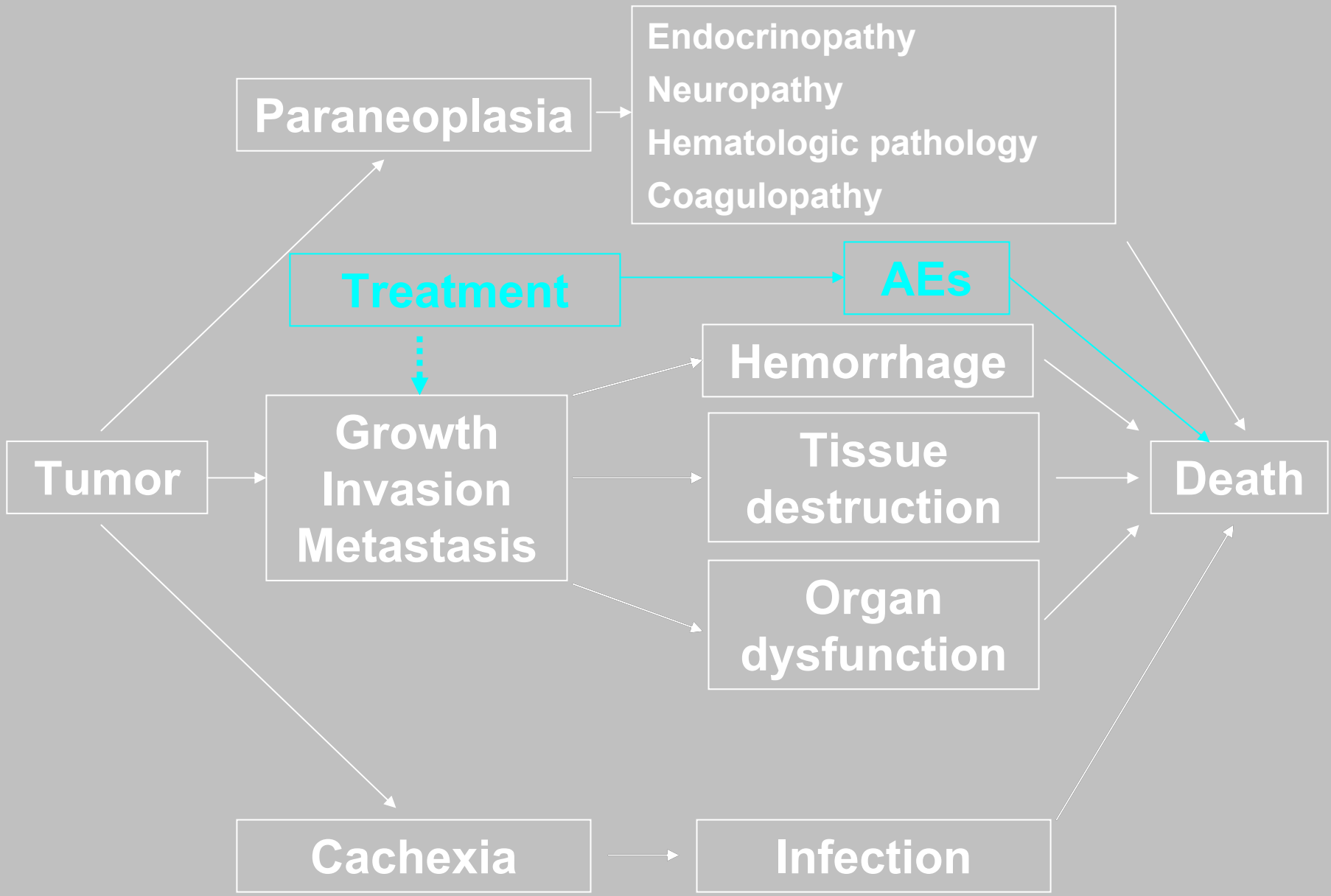
Chaisson R *et al*. Ann Intern Med 1994; 121:905-11

Valid and invalid surrogates





Fleming TR and DeMets D. Ann Intern Med. 1996; 125:605-13


Endocrinopathy
Neuropathy
Hematologic pathology
Coagulopathy
Paraneoplasia
Treatment
AEs
Hemorrhage
Tumor
Growth
Invasion
Metastasis
Tissue
destruction
Death
Organ
dysfunction
Cachexia
Infection

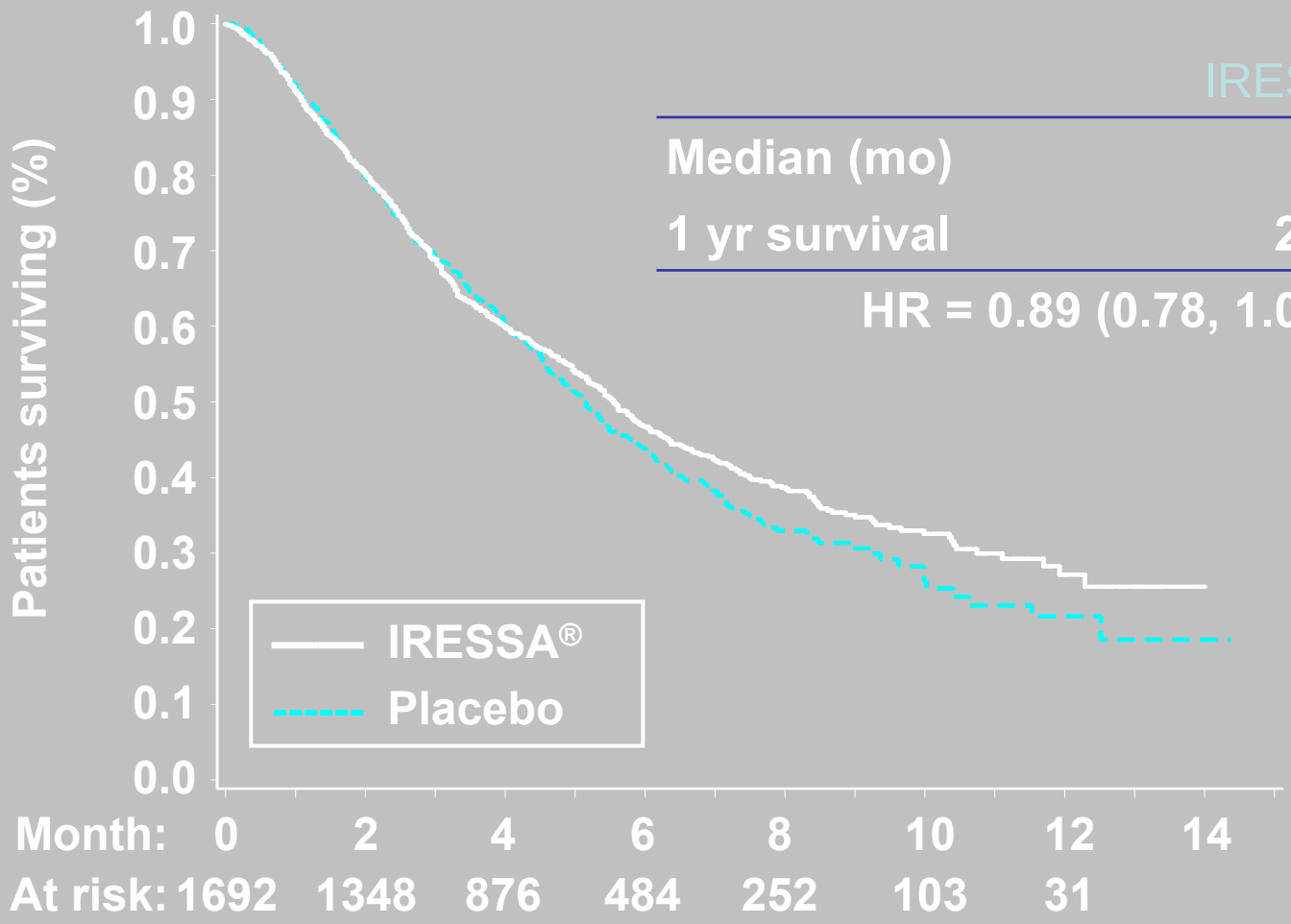
Gefitinib (Iressa)

- 2003: AA for 3rd line treatment of NSCLC
- No benefit in 4 randomized trials in NSCLC
- 2005: distribution limited to patients benefiting/have benefited from gefitinib

Iressa RCT trial: significant ↑ in ORR

	Patients, % (n/N)		Odds ratio	
	IRESSA®	Placebo	(95% CI)	*P* value
Objective response rate	7.7% (74/961)	1.2% (6/483)	7.03 (3.0, 16.4)	< .0001

Iressa CT: No difference in OS



	IRESSA®	Placebo
Median (mo)	5.6	5.1
1 yr survival	27%	22%

HR = 0.89 (0.78, 1.03), *P* = .11

Safety issues

- AA trial may have limited power to detect unforeseen safety problems
- Toxicities may be difficult to analyze, especially in ill patient population in setting of SAT
- Changes in benefit/risk ratio may require labeling changes or restricted distribution

Abarelix: 21 CFR parts 314 and 601 restricted distribution provisions

- GnRH antagonist approved 2003 for advanced symptomatic prostate cancer
- restricted indication and distribution due to risk of anaphylactic reaction and loss of castration effect
- patients in whom benefit > risk (with ureteral obstruction, impending neurologic loss, severe bone pain).

AA frontier: Biomarkers and targeted therapy

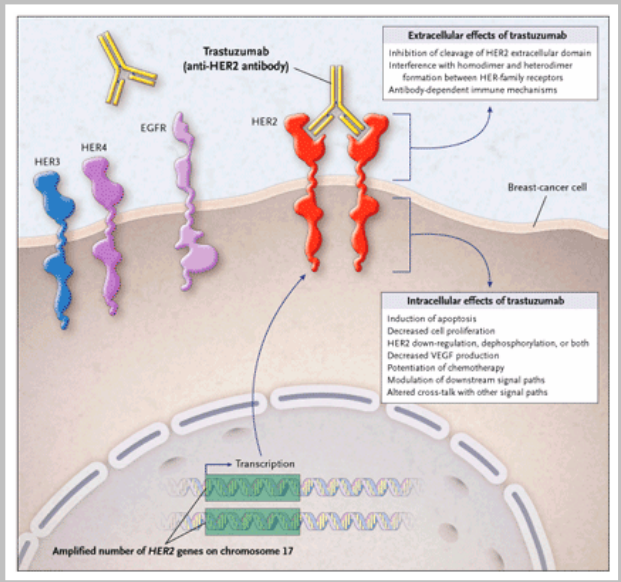
- New "targeted therapies"
  - Re-define definitions of diseases
  - Greater efficacy in selected population may result in smaller patient populations
  - Novel surrogates to be validated
  - Dosing aimed at target rather than MTD
  - Dose studies, chronic administration

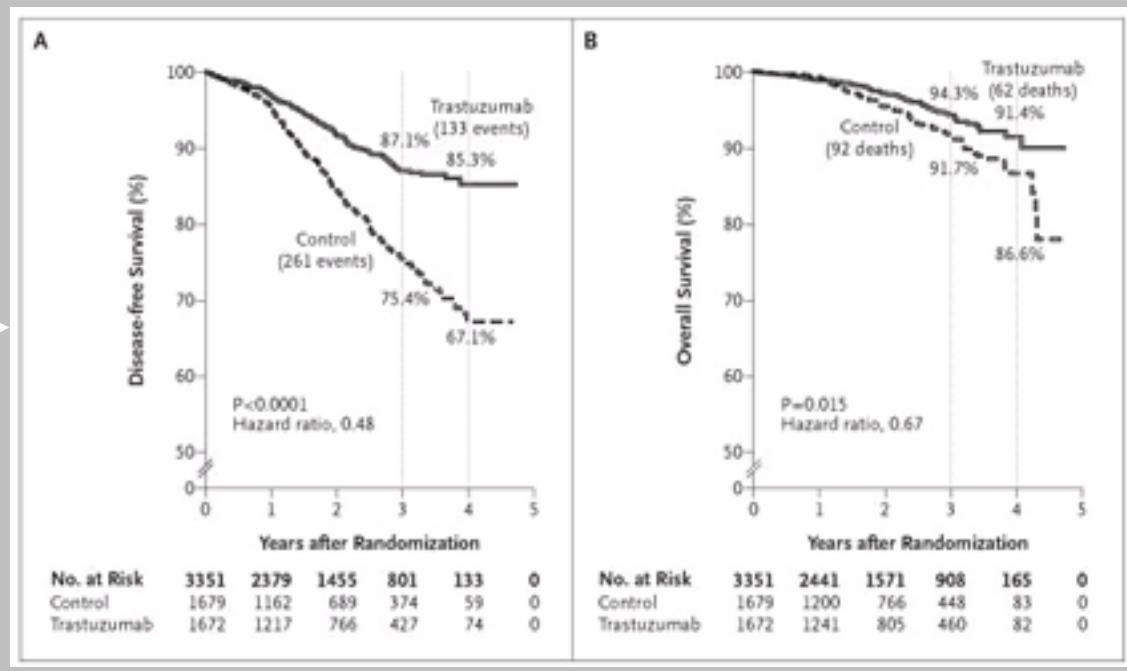
Paradigm shift to targeted anticancer therapy

	Empirical	Targeted
Discovery	Cell-based	Receptor-based
Mechanism	Not identified by screening assay	Basis for selection
Effects	Cytotoxic	Cytostatic
Specificity	Less selective	More selective
Dose/schedule	Cyclical at MTD	Continuous at OBD

Fox E *et al.* Oncologist 2002;7:401

PGx for targeted therapy

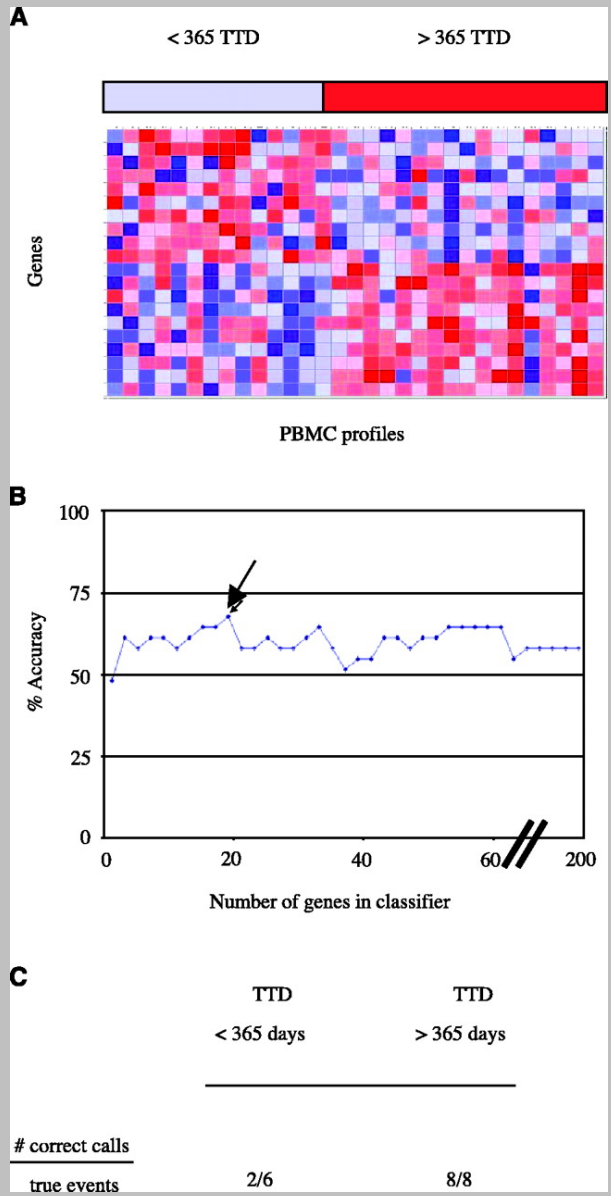




Romond EH *et al.* N Engl J Med 2005;353:1673

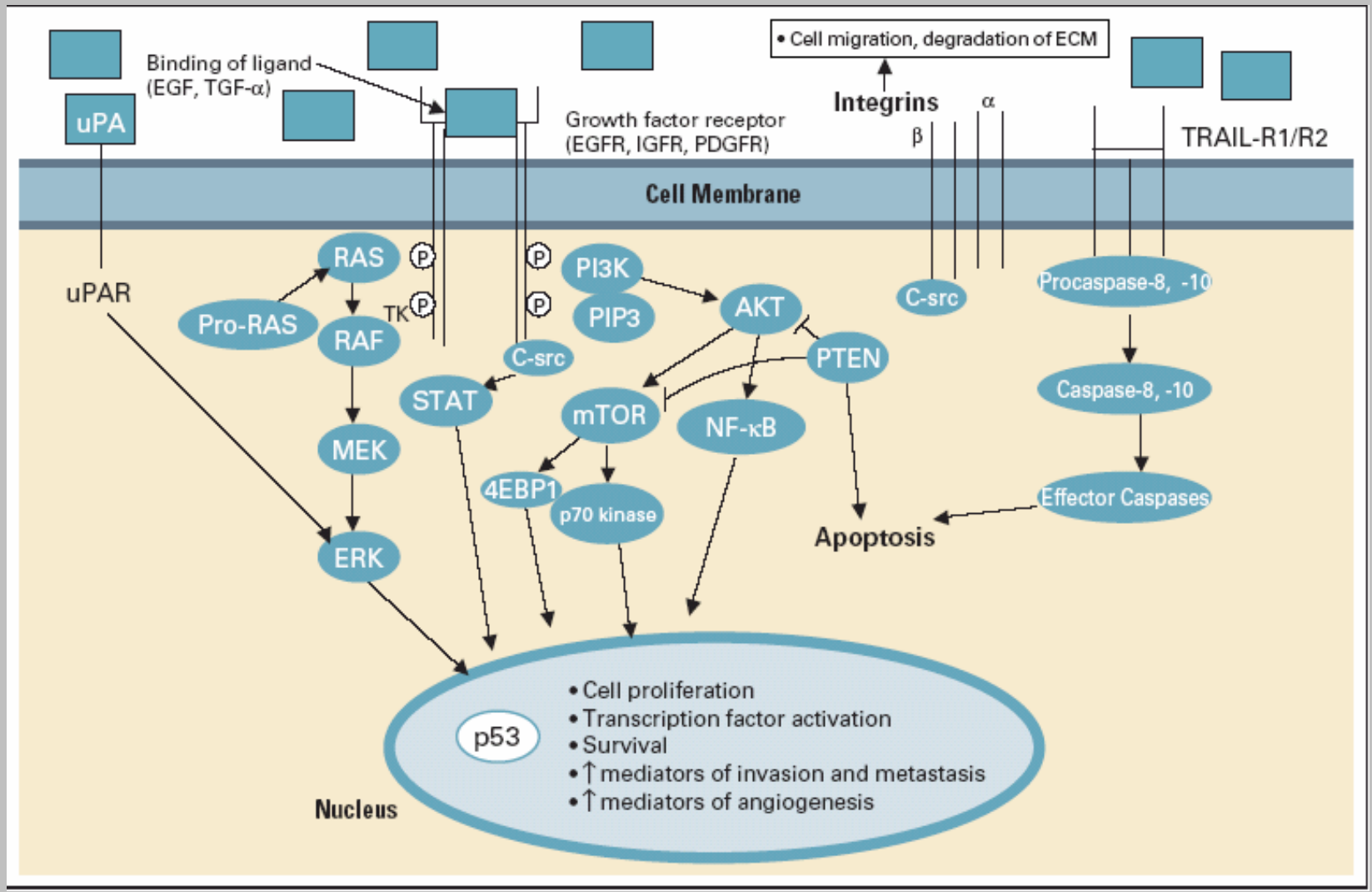
Implications for developmental therapeutics

- Emphasis on PK/PD modeling
- Improved proof-of-concept models
- Potential for more rapid and more efficient lead selection
- Potential for more rapid and more efficient dose selection
- Potential for fewer Phase 3 failures
- Potential new surrogate endpoints



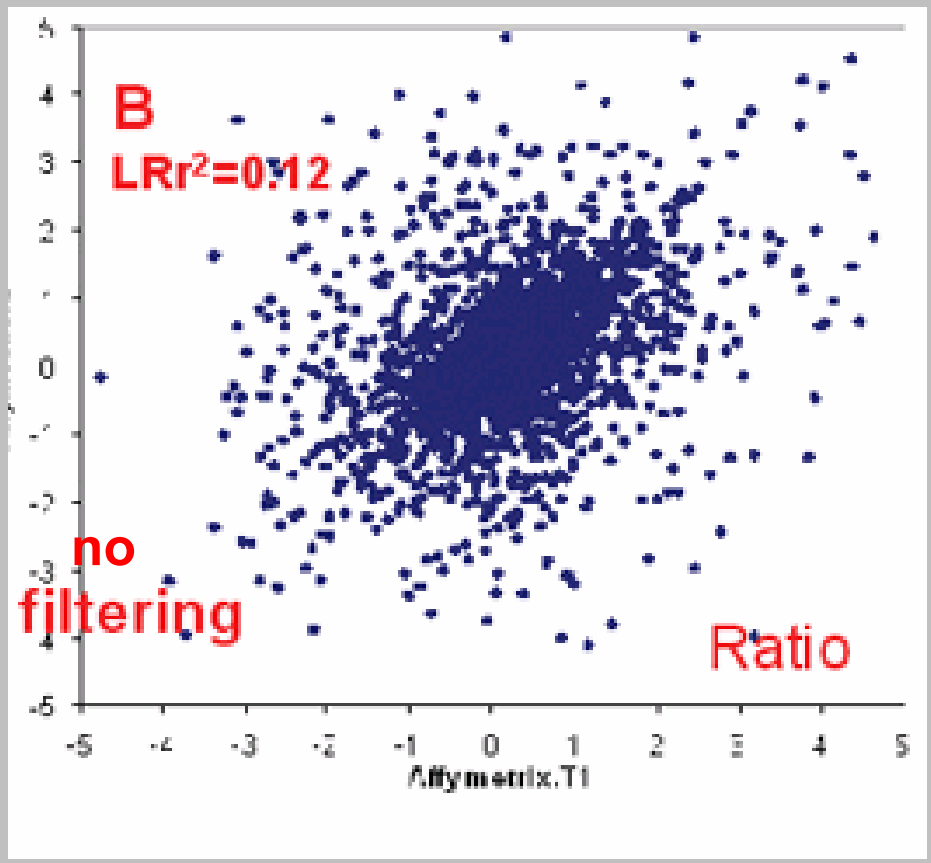
Burczynski, M. E. *et al.* Clin Cancer Res 2005;11:1181

Signaling pathways



Cohen SJ *et al.* J Clin Oncol 2005; 23:5374-5385

Platform variability



Shi L *et al.* BMC Bioinformatics. 2005 Jul 15;6 Suppl 2:S12.

Summary

- Accelerated approval offers a pathway to earlier access to new therapies
- Critical areas to consider include
  - Surrogate endpoint for approval
  - AA trial design
  - Confirmatory trial planning