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FRIENDS of CANCER RESEARCH

Conference on Clinical Cancer Research

Panel Four:

Development Paths for New Drugs with Large Treatment Effects Seen Early

November 10, 2011 • Washington, DC

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Conference on Clinical Cancer Research

Development Paths for New Drugs with Large Treatment Effects Seen Early

Mikkael Sekeres
Cleveland Clinic

November 10, 2011 • Washington, DC

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Development Paths for New Drugs with Large Treatment Effects Seen Early

Jane Perlmutter
Patient Advocate
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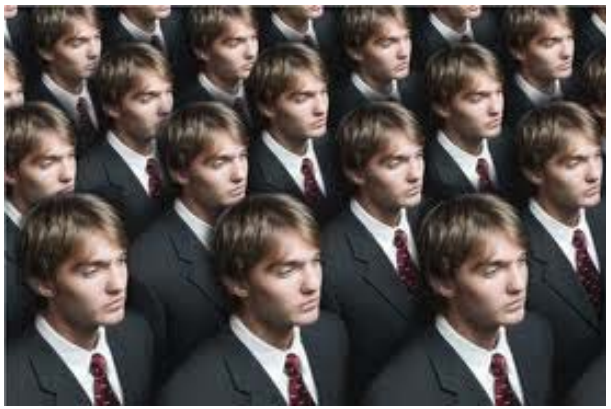
Importance/Public Relevance

Many ***patients*** can not afford ***patience***; neither should researchers or regulators

What Does the Public Want?

- ***We all want the same thing***
  - Highly effective, long-acting therapies
  - Few side effects
  - Manageable costs



What Does the Public Want?

- ***We each have different priorities***
  - Trade offs between length and quality of life
  - Trade offs among severity and length of toxicities
  - Concerns about late-occurring toxicities

Balancing Needs of Current & Future Patients

- Need treatments NOW
- May be willing to try unproven treatments and/or very toxic treatments

- Need well-tested treatments with minimal side effects
- Need current patients to be willing to participate in clinical trials

Large Treatment Effects

Clear Cases

- Potentially curative, or at least long-term chronic disease
- Very likely to be effective in approved target population (e.g., >80%), even if it is a small group
- Limited additional toxicities

Questionable Cases

- Adds weeks or months to life
- Significantly better rate of effectiveness (e.g., doubling)
- Moderate additional toxicities

Alternative Paths to FDA Approval

	Accelerated Approval	Potential New Mechanisms
When Appropriate	• Significant early effects for diseases with limited other options	• Unusually large effects in early trials
Pros	• Make potentially useful new agents rapidly available to patients with limited options • Provide early opportunity for developers to receive reimbursements • Provide additional assessment of safety (including late occurring toxicities) and efficacy	• Make potentially useful new agents rapidly available to patients with limited options • Provide early opportunity for developers to receive reimbursements • Eliminate the need to randomize additional patients
Cons	• Require additional randomization of patients	• Provide little opportunity to identify late-occurring toxicities

Challenge
Think Outside the Box

Challenge	***Potential Solution***
• Ethical and practical issues accruing patients to randomized trials once new agents become available	• Unbalanced and/or adaptive randomization designs; registration trials
• Increasingly small populations	• Decision Analysis
• Difficulty dealing with multiple outcomes	• Bayesian Approaches

2011 Conference on Clinical Cancer Research

Potential Approaches for Large Treatment Effects Seen Early in Development

November 10, 2011

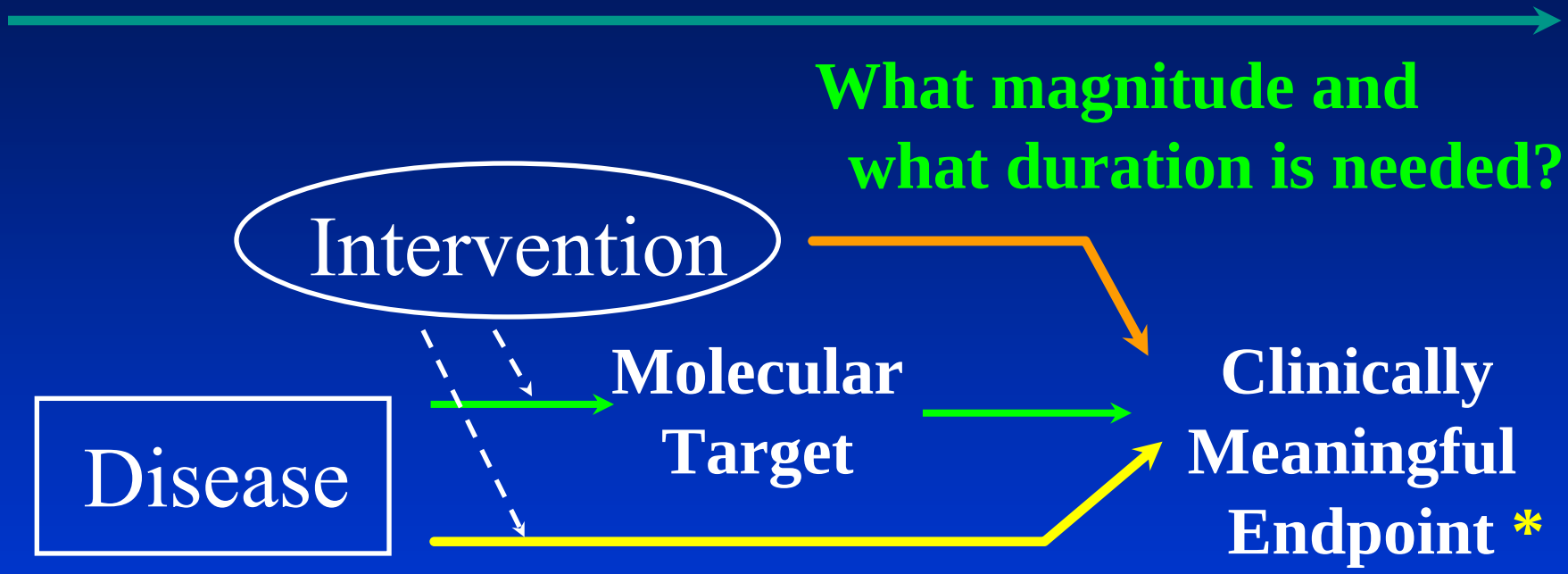
Thomas R. Fleming, Ph.D.

Professor of Biostatistics
University of Washington

tfleming@u.washington.com

Fleming TR, Richardson BA. *JID* 190(4): 666-674, 2004

Mechanisms of Action of the Intervention & Causal Pathways of the Disease Process



* IOM (2010) & Temple (FDA): Direct measures of "feels, functions or survives"

Development Strategies

After Phase 1

…if early results are very favorable…

What should be the next step?

~ **Phase 2b: (Randomized Screening Trial)**

…if true effect is *moderate*

~ **Phase 3: (Randomized Registration Trial)**

…if true effect is *very large*

Development Strategies

~ **Phase 2b: (Randomized Screening Trial)**

…if true effect size is *moderate*…

~ Phase 3: (Randomized Registration Trial)

…if true effect size is *very large*…

Some properties:

- Randomization ⇒ Assessments not limited to:

  tumor response, for single agent regimens

  …E.g., Can assess OS, PFS, PROs, (i.e. regis. endpoints)

  for either single agent or add-on regimens

- Confidentiality of interim results reduces pre-judgment

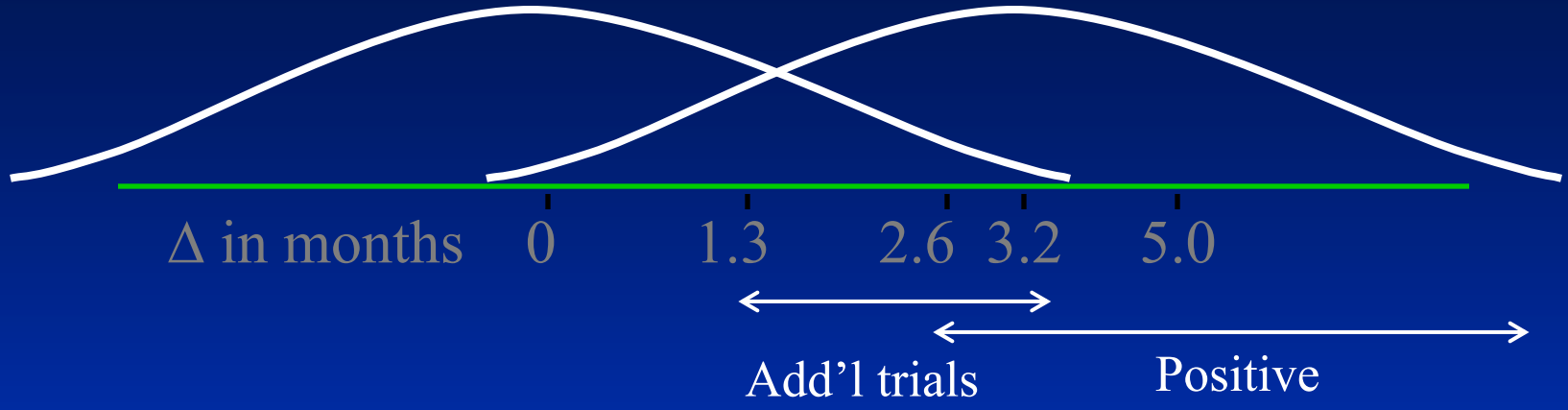
Statistical Principles

- Goals for Phase 2b screening trial
  - ~ Large enough to support proof of concept
  - ~ Small enough to be a measured step before Phase 3
- Assumes identical Phase 2b and Phase 3 endpoints
- For illustration, assume
  control arm median is 6 months
  - ~ Likely realistic for
    Survival in 2nd or 3rd line NSCLC
    PFS in 1st & 2nd line Breast Cancer
    Survival in 1st line Pancreas Cancer
  - ~ Will require adjustment for different settings; principles remain

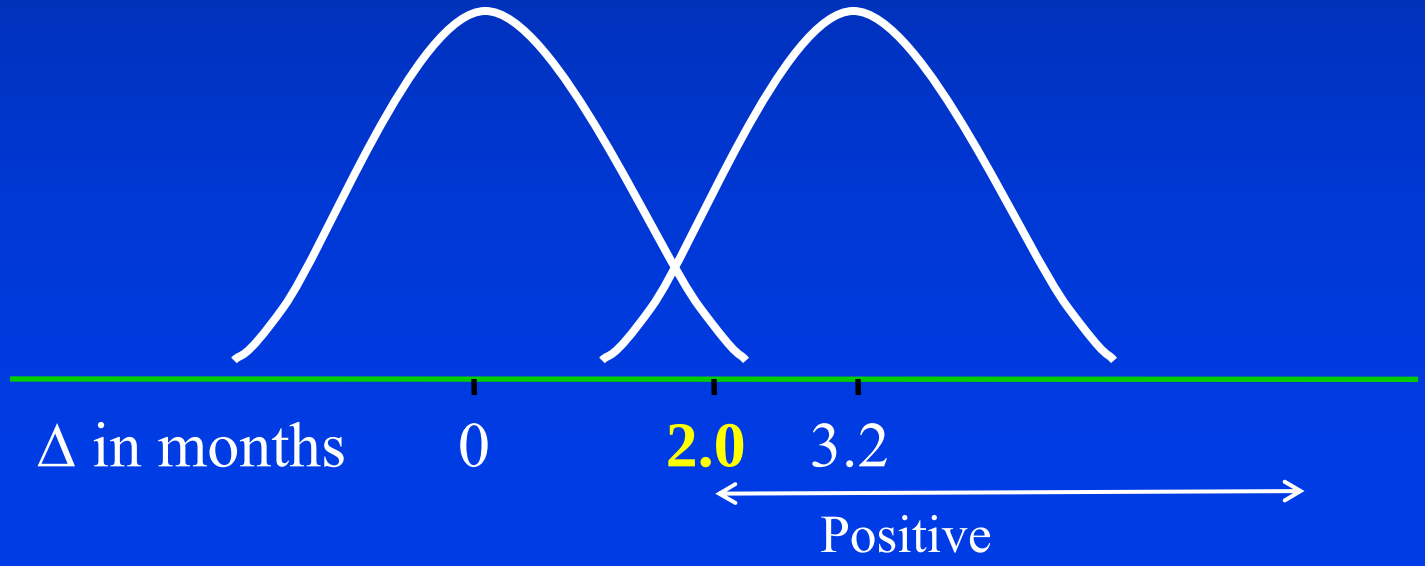
Phase 3 Design Considerations

- Illustration:
  - Suppose a 6 vs. 8 month improvement is the smallest benefit of clinical significance…
  - In turn, the trial should have 90% power to detect a true RR=0.65 (a 6 vs. 9.2 month difference)

Outcome Probabilities – Phase 2b Trial Design, (120 events)



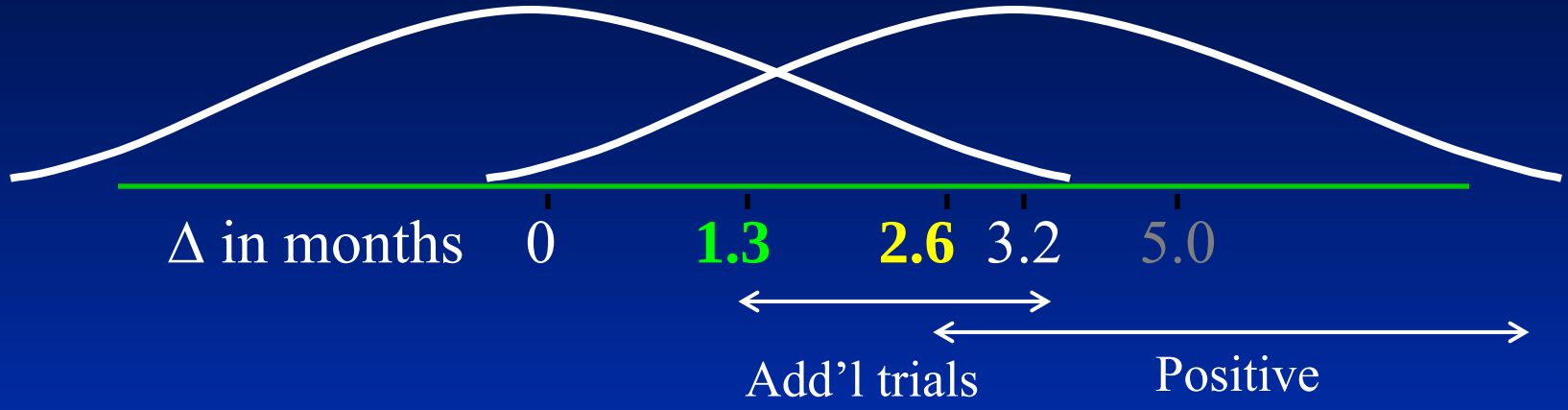
Outcome Probabilities – Phase 3 Trial Design, (451 events)



Phase 2b Trial Considerations

- Objective:
  - ~ Maintain low (i.e. 10%) false negative error rate while allowing a 10% to 15% false positive rate
- Target sample size:
  - ~ ¼ the size of a stand alone registrational Phase 3 trial (i.e., ¼ of an SOE2 trial)
- 120 events (approx. 451 * .25)

Outcome Probabilities – Phase 2b Trial Design, (120 events)



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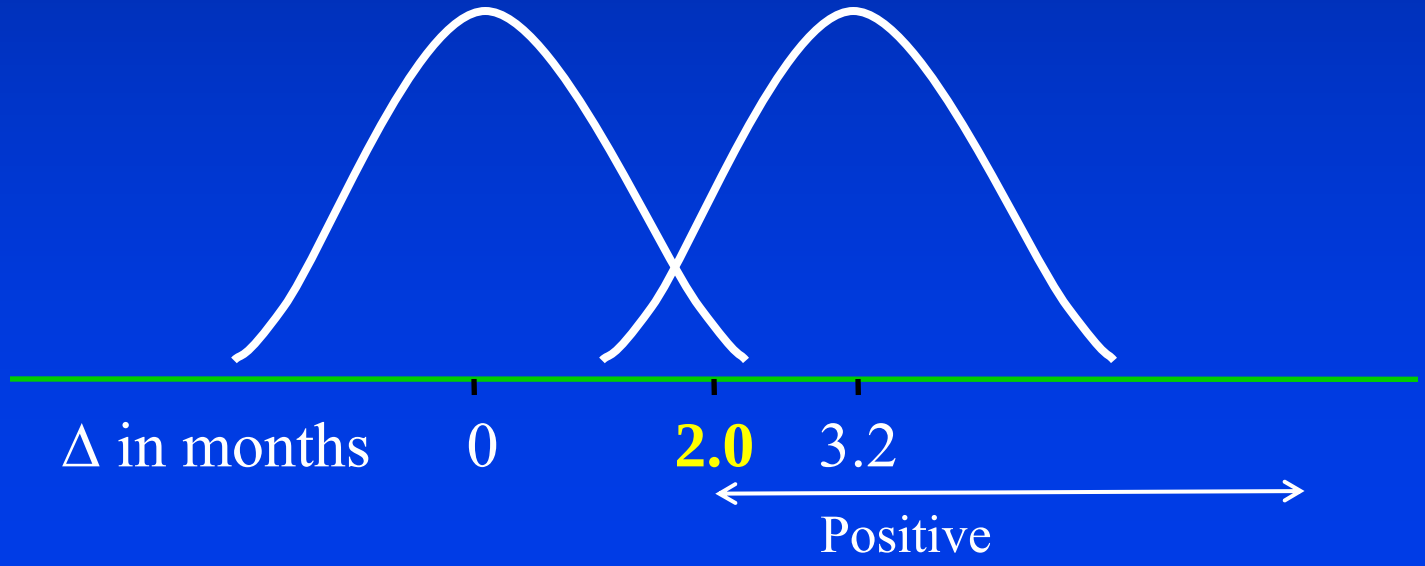
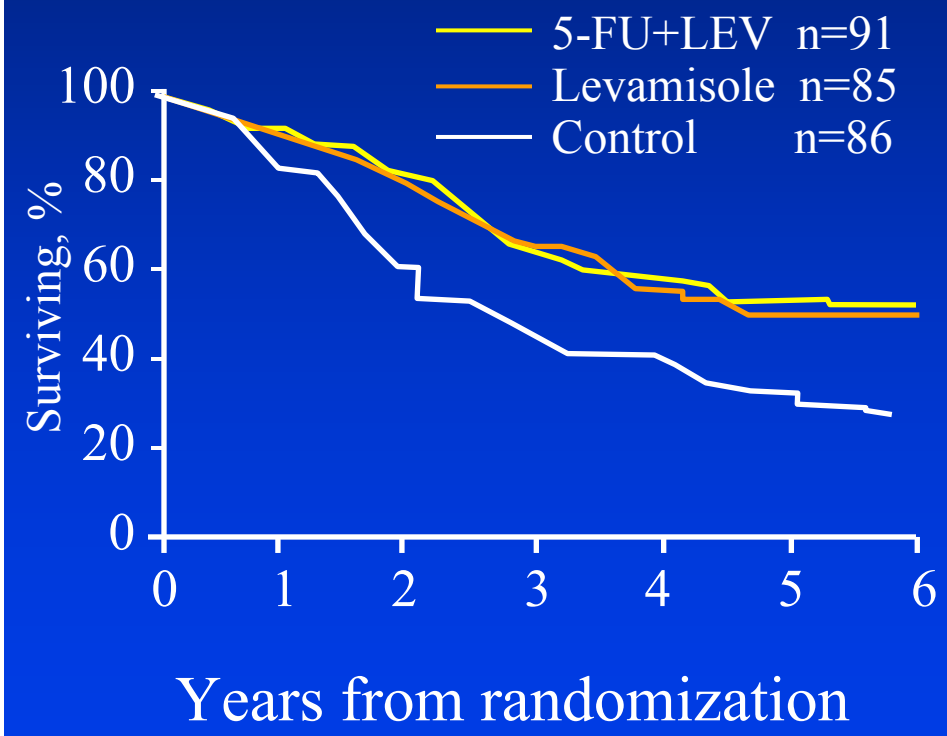


Phase 2b Sample Size & Duration

- Total sample size for the trial: 2N = 220
  - ~ 120 events;
  - Prob. stat sign: **66%** if true RR = 0.65 (i.e. Δ = 3.2 mo)
  - ~ Rule out ineffective indications with **86%** probability
  - ~ Rule in effective indications with **90%** probability
- 8 month duration of enrollment
  - …Assume enrollment 28 patients per month
- 4 additional months of follow-up
- Data available for analysis approximately one year after initiation of enrollment

SURGICAL ADJUVANT THERAPY OF COLORECTAL CANCER

NCCTG Trial



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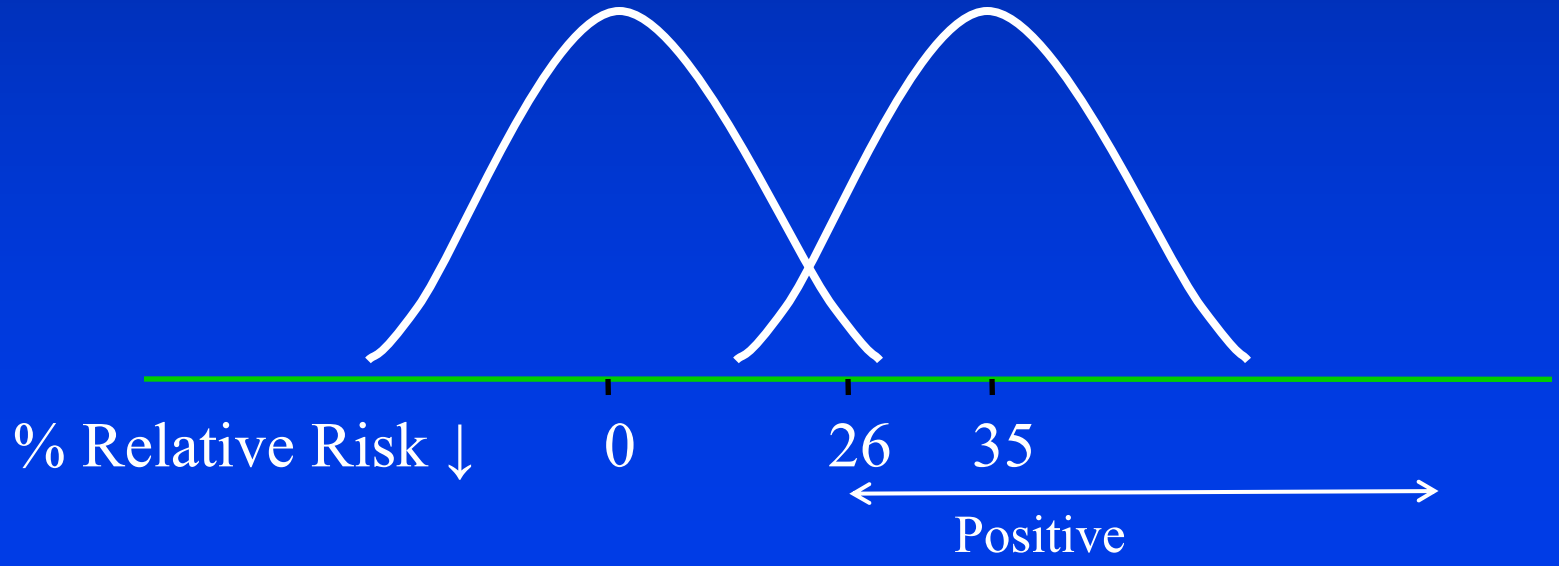

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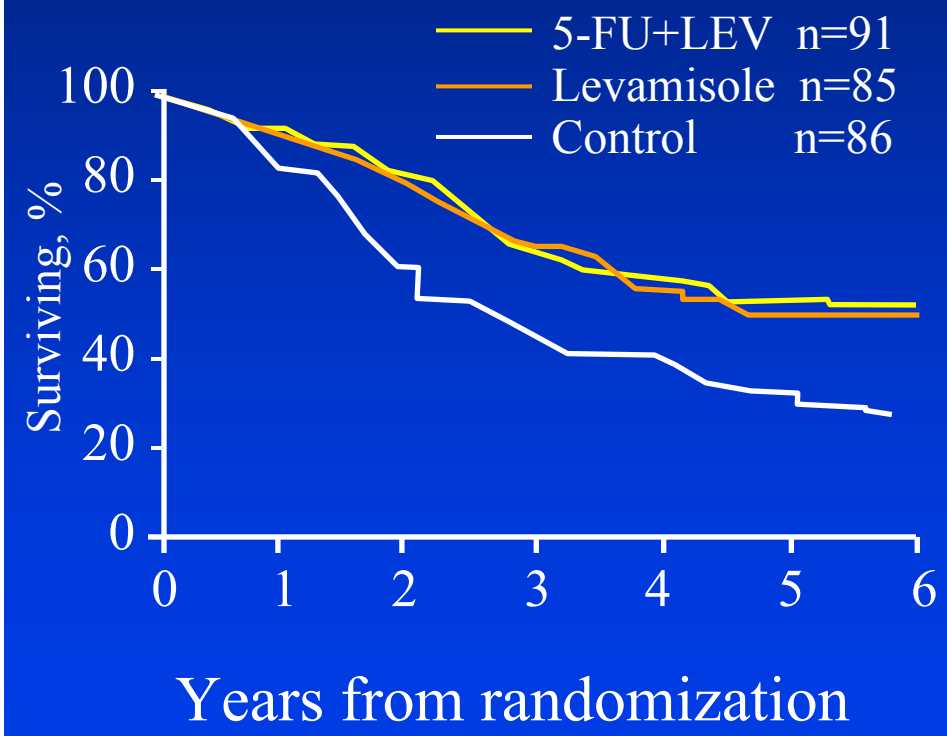

Cancer Intergroup Trial

SURGICAL ADJUVANT THERAPY OF COLORECTAL CANCER

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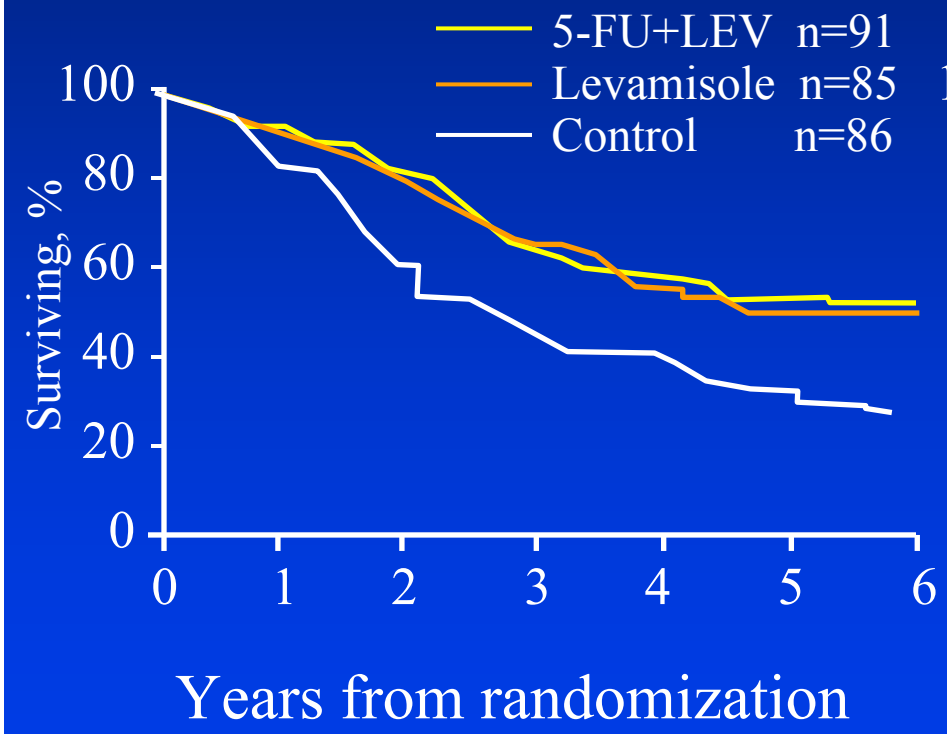
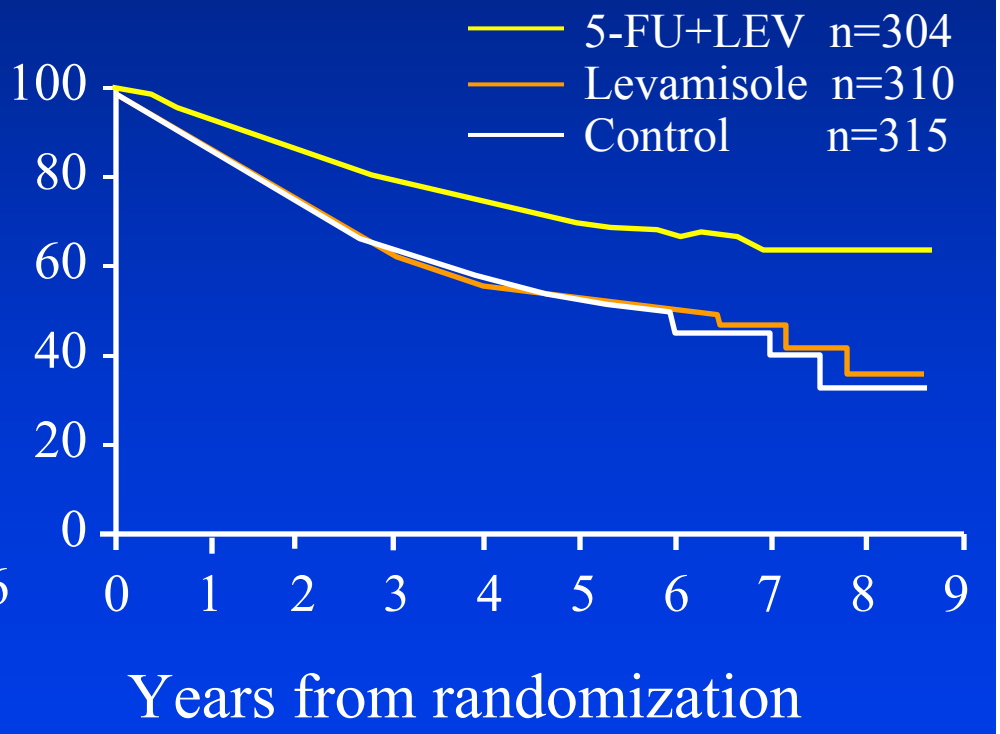


Cancer Intergroup Trial



Statistical Summary

- Phase 2b designed
  with subsequent Phase 3 in mind
- Goals:
  - ~ to screen out ineffective indications, &
  - ~ to screen in the effective indications
    with high probabilities
- If "signal" seen, requires confirmation in Phase 3
  - – Probability of Phase 3 success therefore enriched
- *Strongly favorable evidence from Phase 2b could allow consideration of registration…*

Development Strategies

After Phase 1

…if early results are very favorable…

What should be the next step?

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…if true effect is *moderate*

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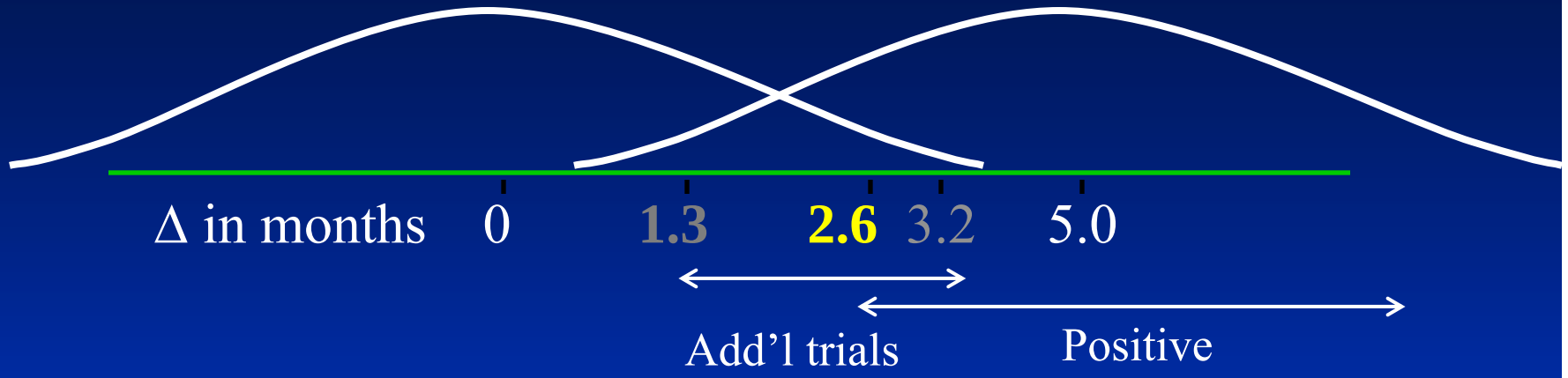

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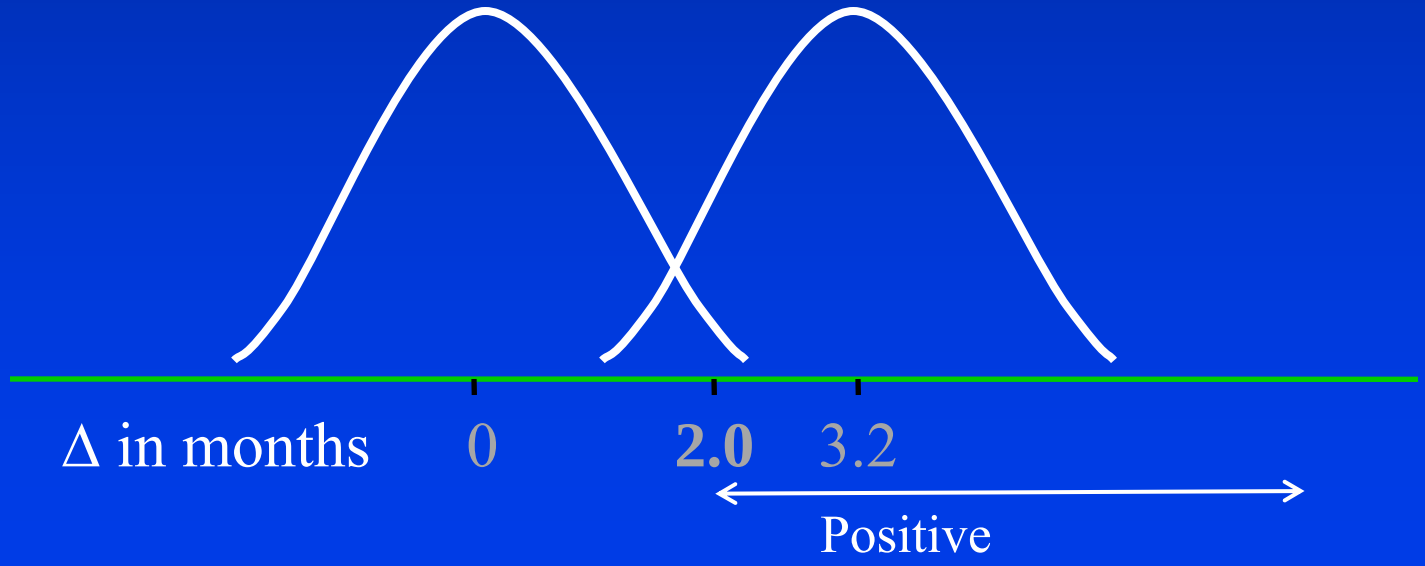
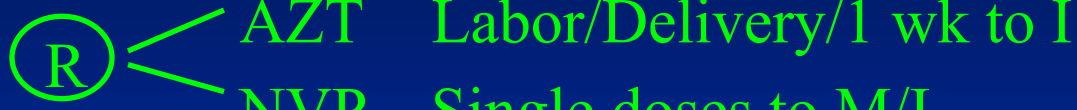


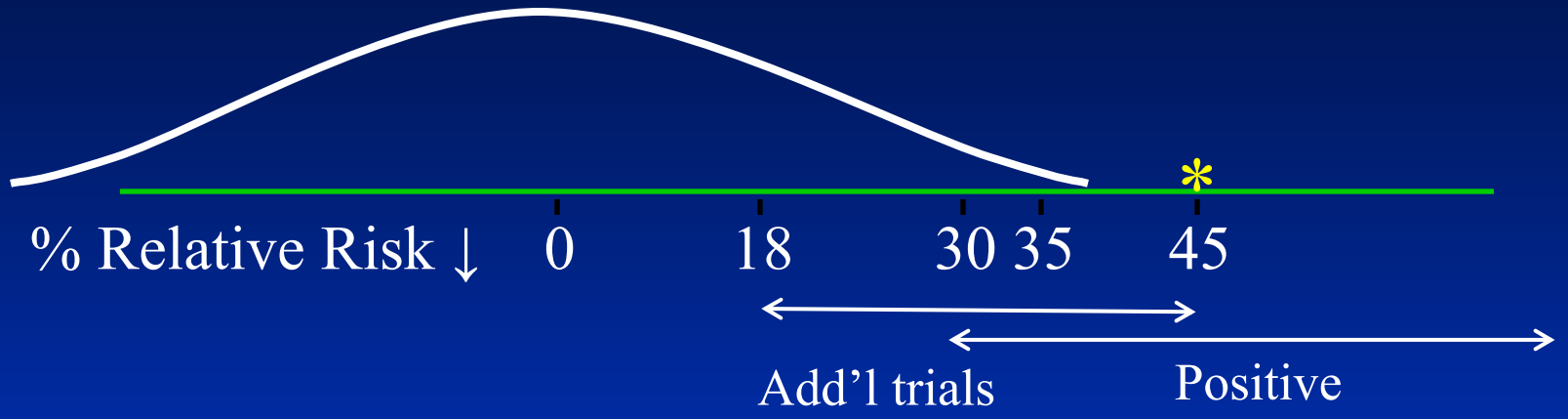
Illustration of a Phase 2b Trial with "Compelling" Results: HIVNET 012



- Results *Lancet* 1999; 354: 795-802

		MCT of HIV	
	N	6-8 wks	14-16 wks
AZT	302	59 (21.3%)	65 (25.1%)
NVP	307	35 (11.9%)	37 (13.1%)
		1p = 0.0014	1p = 0.0003

Outcome Probabilities – Phase 2b Trial Design, (102 events)



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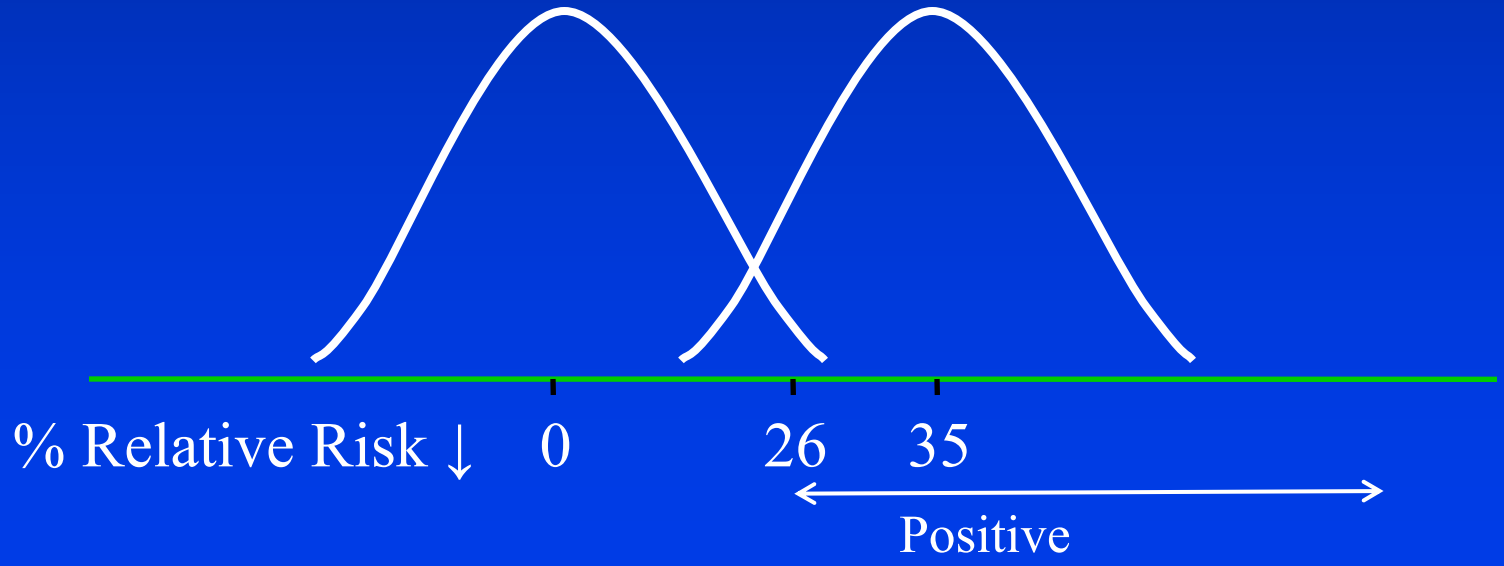

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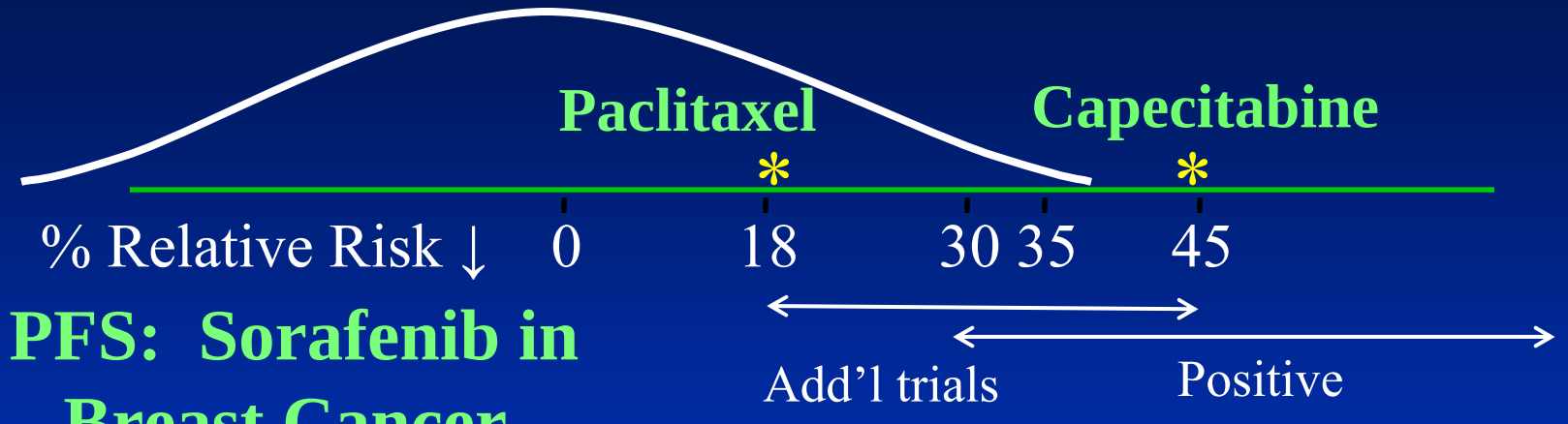
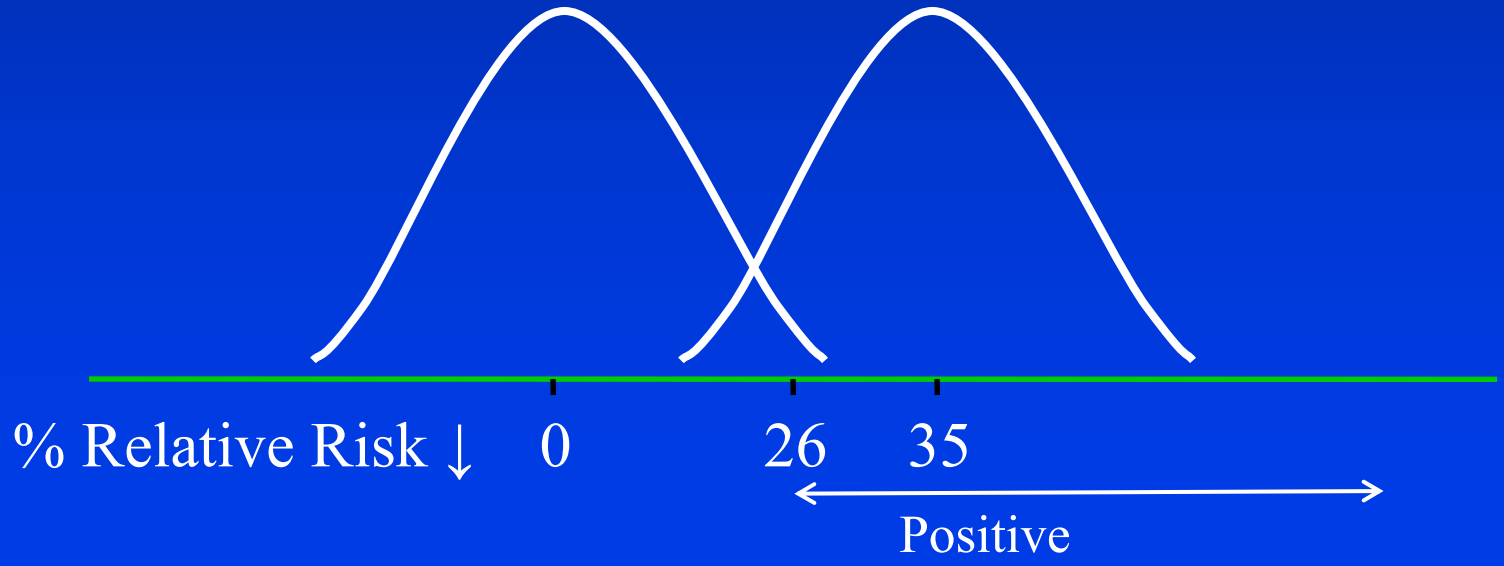


PFS: Sorafenib in Breast Cancer

Outcome Probabilities – Phase 3 Trial Design, (451 events)



Development Strategies

~ Phase 2b (Randomized Screening Trial)

…if true effect size is *moderate*…

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Some properties:

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Janet Woodcock
FDA

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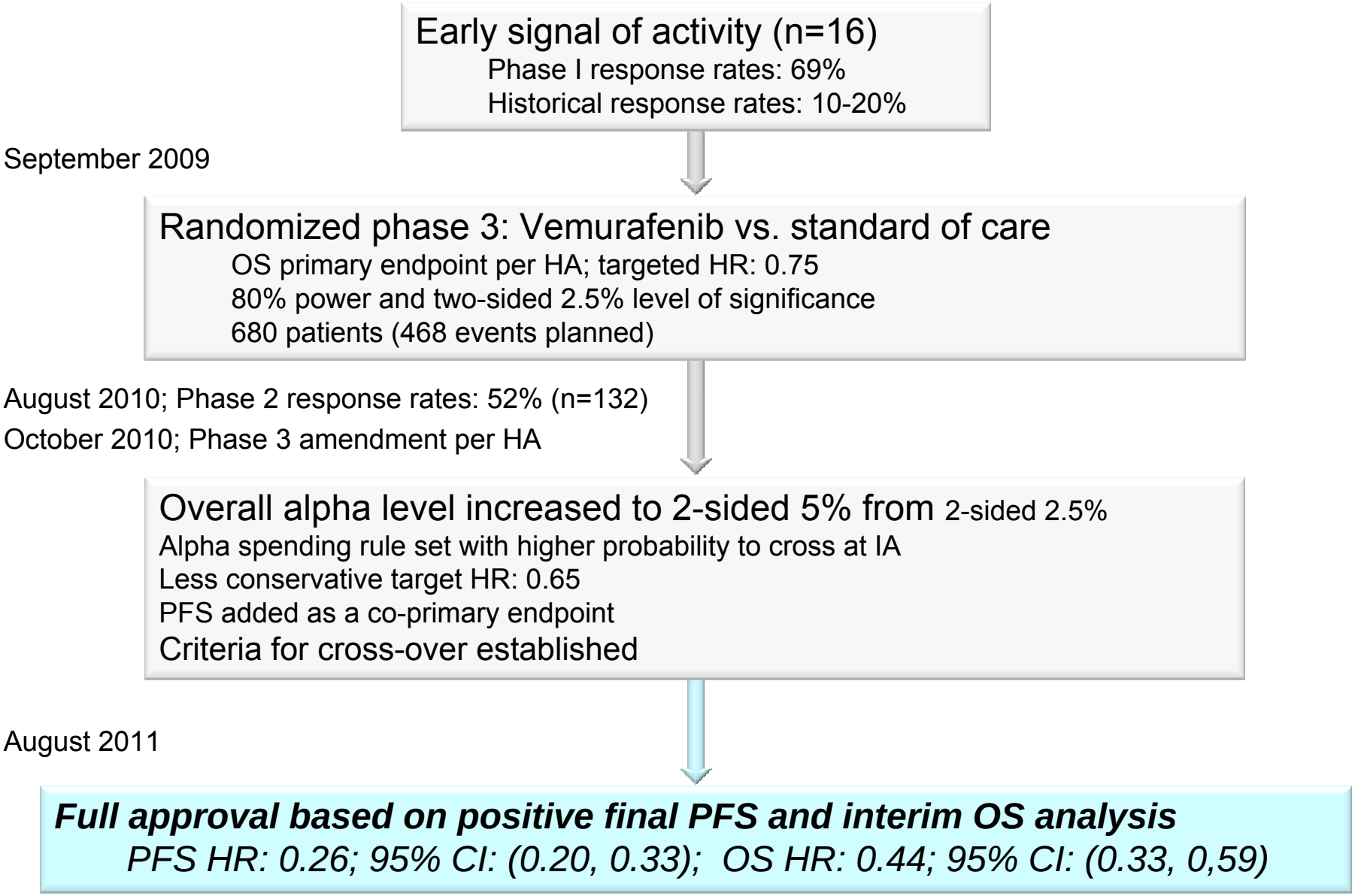
Case studies/Industry Perspective

Gracie Lieberman

November 10, 2011

Vemurafenib in V600E BRAF Melanoma



Crizotinib in ALK Positive Advanced NSCLC

Early signal of activity (n=14)
- Phase I response rates: 50%
- Historical response rates: 10-20%
- Phase I protocol amendment

April 2009

End-of-phase II meeting:
- Observed data: 57% ORR in N=82 ALK-positive NSCLC patients
- Options for Accelerated Approval Discussed; Randomized phase III recommended by HA
- AA could be granted on interim analysis of a surrogate endpoint

April 2010

HA interaction:
- Can 2 single arm studies support AA with 1 confirmatory trial
- HA response: review issue

July 2010: General pre-NDA meeting

August 2011

Accelerated approval based on 2 single arm trials; ORR: 50% - 60%; median duration of response 40 – 50 weeks

Confirmatory studies with PFS as primary endpoint are ongoing

Cross-over is allowed

Vemurafenib and Crizotinib – The Fleming Proposal

Early signal of activity (n < 20)
- Phase I response rates: 50% - 60%
- Historical response rates: 10-20%

Need to confirm activity before phase II or HA interactions

Randomized phase II: NME vs. SOC

OS primary endpoint: Screening target HR=0.65
- Ex. 150 patients (98 events); study duration: 18 months
- or 200 patients (112 events); study duration: 16 months

No cross-over; full approval is the goal

Pre-specified targeted HR < 0.5 observed

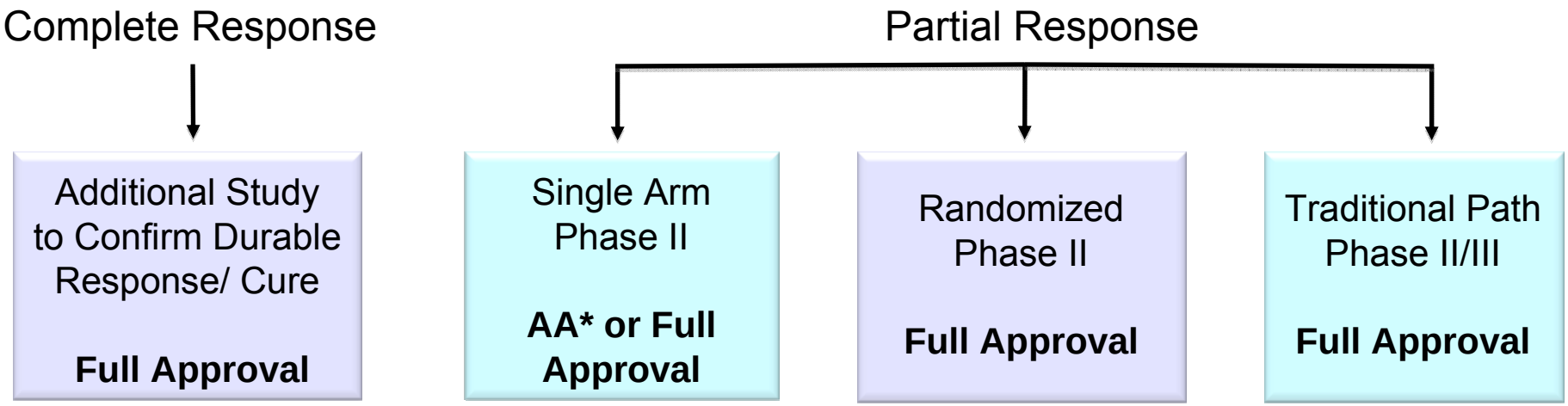
Full approval

Pre-specified targeted HR not observed but still clinically meaningful ORR confirmed and >> control

Accelerated approval

Industry Considerations for Development Paths

Large treatment effects observed early



* May or may not require randomized confirmatory study

Industry Considerations for Development Paths

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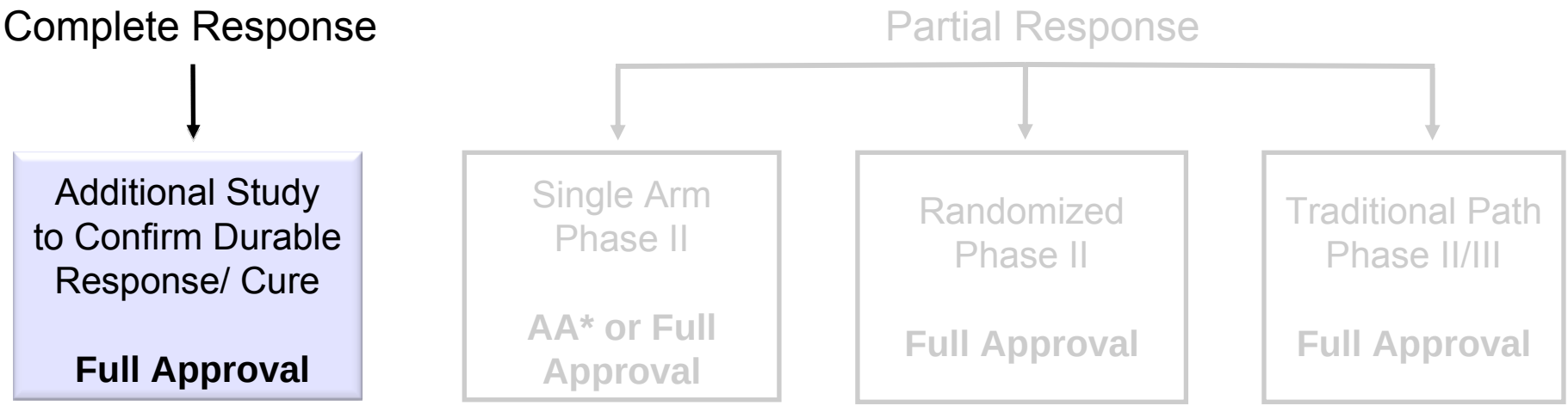
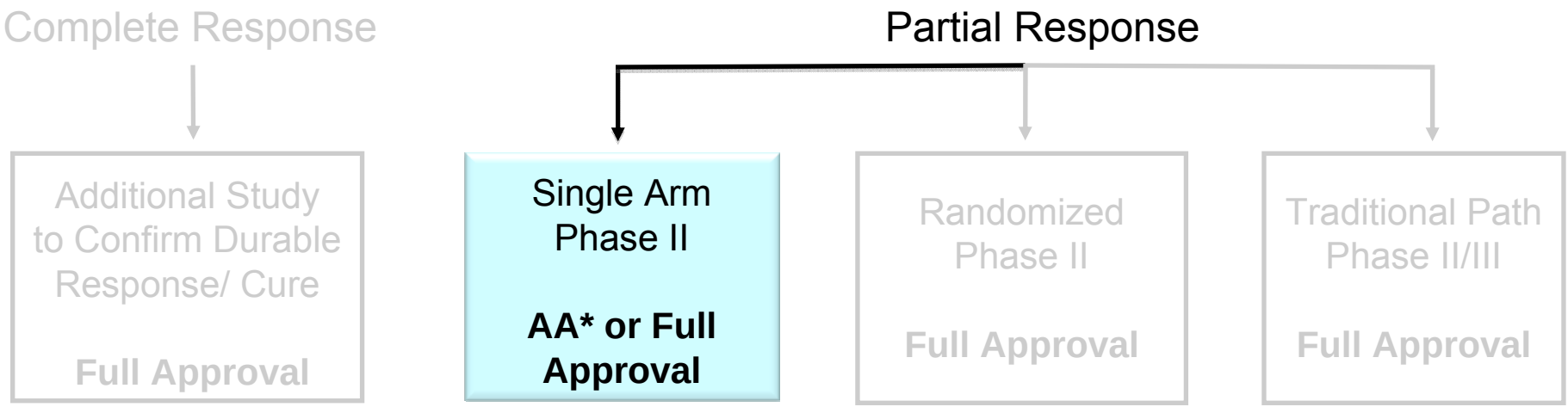


- Rate of complete response
- Confirmation of response
- Duration of response

Industry Considerations for Development Paths

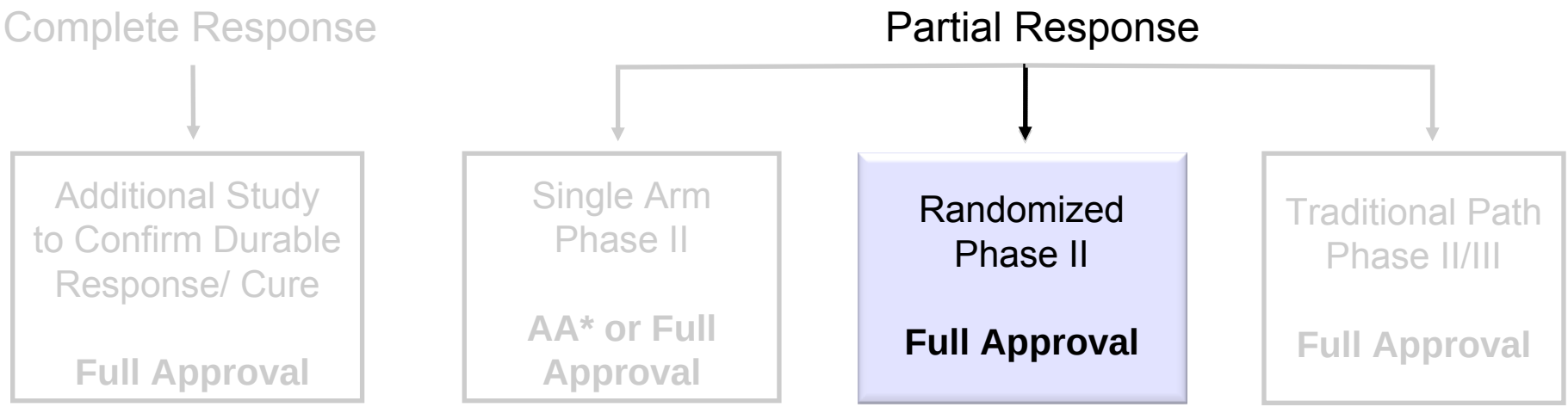
Large treatment effects observed early



- Rate of overall response
- Confirmation of response
- Duration of response
- Historical outcomes
- Feasibility to conduct confirmatory study if AA
- Clarity when randomized confirmatory studies will be required
- Acceptance of single arm studies and ORR endpoints in global environment

Industry Considerations for Development Paths

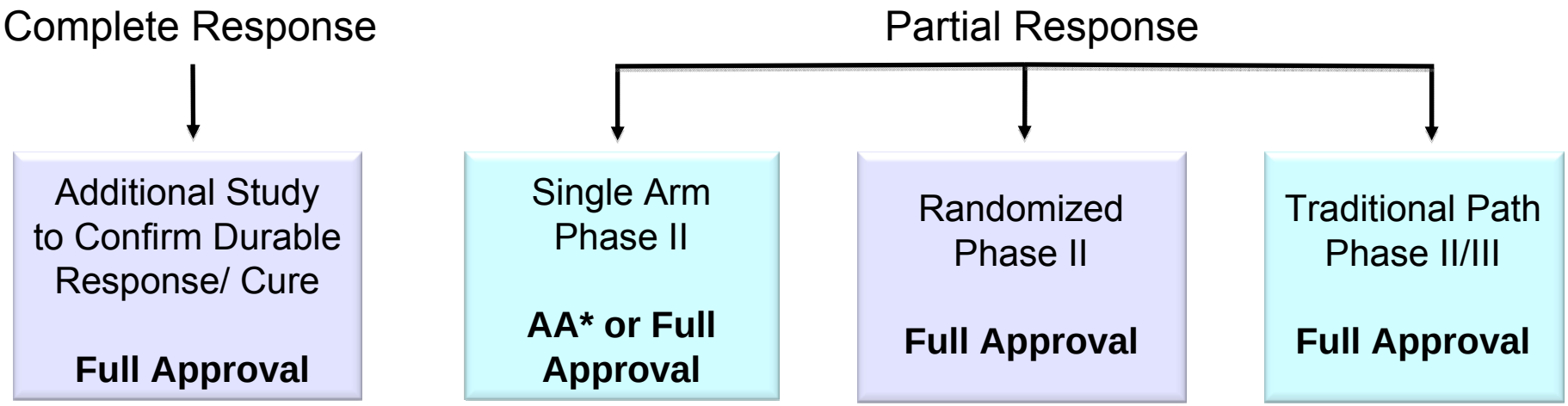
Large treatment effects observed early



- Rate of overall response
- Confirmation of response
- Duration of response
- Historical outcomes
- Translatability of ORR into clinical benefit
- Clarity of what “success” means
- Operational complexity of conducting the study
- Acceptance of small randomized studies in global environment
- Primary endpoint PFS with cross-over or OS with no cross-over

Industry Considerations for Development Paths

Large treatment effects observed early



Question: Could early treatment effects observed in vemurafenib and crizotinib qualify these drugs for accelerated approval based on single arm phase II followed by single arm confirmatory trial ?

Question: How many exposed would be required to determine and agree on path forward ?

* May or may not require randomized confirmatory study

Points to Consider for Guidance

Providing "breakthrough" drugs to patients sooner will require clear guidance

Guidance needs to provide a new path to enable expedited conversations/agreements

Guidance needs to provide clarity on

- **Definition of poor outcomes**
  - Relative to the observed/expected benefit of the new therapy
- **Processes for diagnostics**
  - Data required for approval of diagnostics
  - Drug approval without commercially available diagnostics
- **Process when commercial product not final**
  - Post-marketing bridging studies for new formulation
- **Agreements on risk sharing**
  - Feasibility/conduct of PMC

Back Up

Iniparib in Triple Negative BC

Early signal of activity (n=14)?

Limited single agent activity in phase Ia

Randomized, open label phase II (n = 123)

Iniparib + SOC vs. SOC

Cross-over allowed

ORR: 52% vs. 32%; PFS: 5.9 vs. 3.6 months; OS: 12.3 vs. 7.7 months

Randomized, open label phase III (n = 519)

Iniparib + SOC vs. SOC

Cross-over allowed

PFS: 5.1 vs. 4.1 months; OS: 11.8 vs. 11.1 months

What went wrong:

Imbalance in prognostic baseline characteristics;

Scientific plausibility

Study conduct: was phase II biased?

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Wyndham Wilson
NCI

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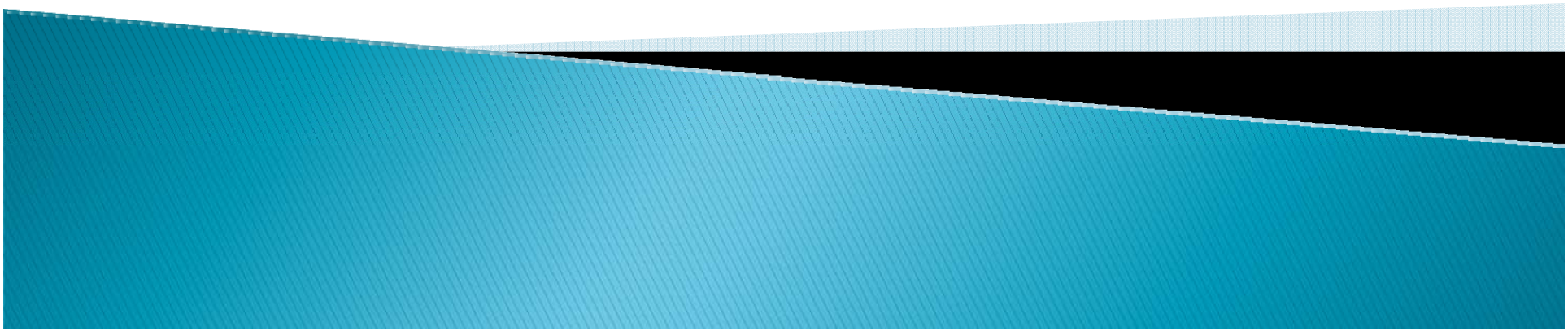
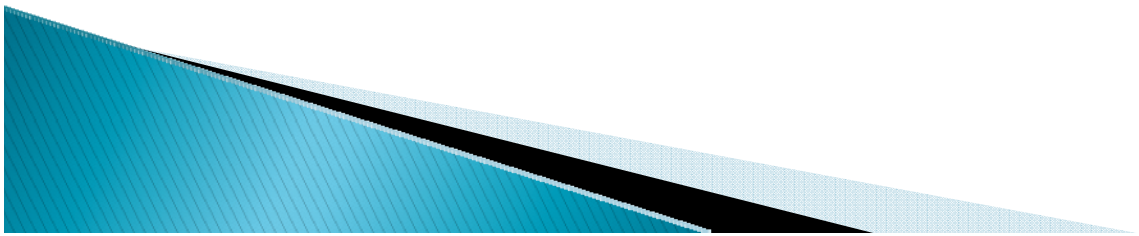
Development Paths for New Drugs



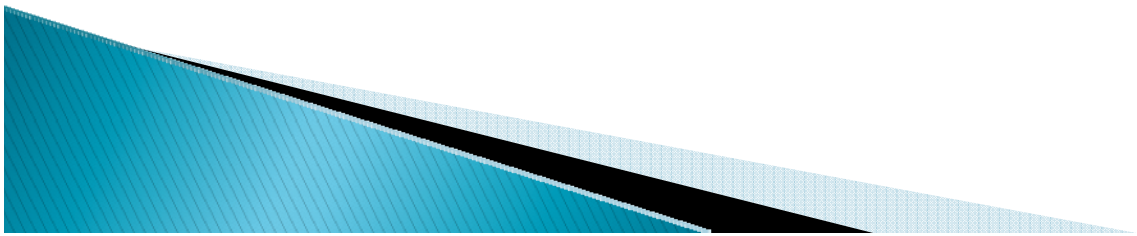
Early Considerations of Full Approval

- Not a solution to the problem
  - Limits efficacy and safety data
  - Discourages company sponsored follow up trials
  - No advantage to patients



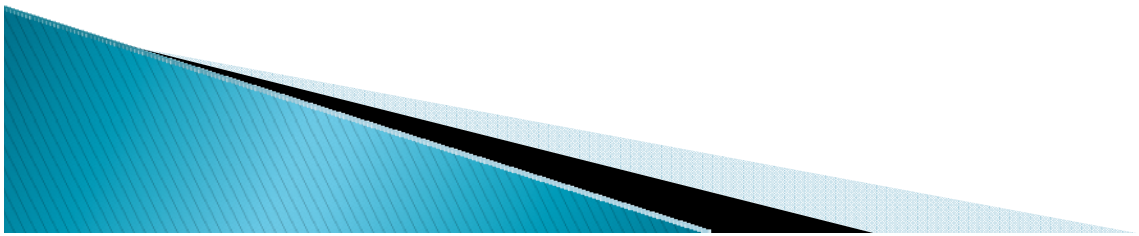
Considerations for Accelerated Approval

- Modified criteria to increase drug approval
  - Modify requirement that drugs show activity after failure of approved agents.
    - Limits ability to conduct trials
    - Assumes a drug is only beneficial if active in a new space
    - Limits approval of new drugs, which may show important uses in post-marketing trials
    - Criteria should focus on approval of active agents with balanced risk-benefit, particularly if a new drug class



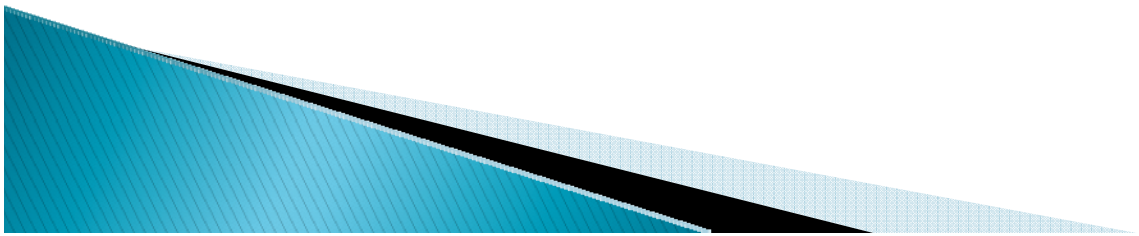
Considerations for Accelerated Approval

- Modified criteria to increase drug approval
  - Provide pathway for approval of combination agents
    - One or both may not have FDA approval overall or for indication
    - Scientific evidence that agents target multiple points in a driver pathway–in vitro synergy
    - Single agent and combination safety
    - High durable response rates for combination



Considerations for Accelerated Approval

- Strict adherence to confirmation of efficacy and safety in post-approval trials
  - Required milestones with real penalties
  - Active surveillance of trial progress
  - Required withdrawal of indication if clinical benefit/safety is not confirmed or trials are not timely
  - Ability to challenge withdrawal based on “legal” criteria should be addressed within FDA policy. Non-clinically based challenges places the accelerated approval process and patient safety at high risk



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Edward Korn
NCI

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Panel 4:
Development Paths for New Drugs with Large Effects Seen Early

Dr. R. Sridhara
Director, Division of Biometrics V
CDER, FDA

Large Effect Seen Early

- Large Effect Definition?
  - Knowledge of disease course
  - Disease dependent
  - Available therapy
  - Availability of historical data
  - You know when you see it?
- Seen Early
  - Chance?, Over estimate?, Safety?

Proposed Designs

- Single arm studies
  - Monotherapy
  - Rare diseases
  - Magnitude and duration of response
  - Limited safety data, Benefit >>> Risk
  - Historical data unavailable in biomarker based subgroup
  - Biomarker a prognostic marker - better risk population in the study
  - Small sample size – lack of confidence in the estimates
    - Vemurafenib example: Ph 1 extended phase 26/32 (81%) responders, 95% CI: 64%, 93%). Ph 2 study 69/132 (52%) responders, 95% CI: 43%, 61%).
  - Valid biomarker – Approved test?

Proposed Designs

- Phase II RCT
  - Monotherapy or combination
  - Limited safety data, Benefit >>> Risk
  - Huge differences can be observed with small sample size – lack of confidence in the estimates? Replication?
    - Iniparib example
  - Valid biomarker – Approved test?

Summary

- Exploratory Studies: less restrictive, generate hypothesis
- Confirmatory Studies: Hypothesis testing controlling false positive conclusions
- Single arm studies with substantial response and duration of response in rare diseases
- Proposed Ph 2
  - A confirmatory study for large treatment effect,
  - Futility study if early effect was by chance, and
  - For moderate effect – could consider planned adaptation to increase sample size.
  - Simulation of different decision possibilities is critical before start of study

Summary

- RCT allows to evaluate products despite gaps in historical knowledge, controls confounding due to known and unknown factors, provides both comparative efficacy and safety for benfit:risk evaluation
- Large effect is a moving target
- Consult FDA if large effect is observed in early development for future design of studies