

Phase II Cancer Trials: When and How

**NCIC CTG Course for New Investigators
August 21-23, 2013**

Acknowledgment

- Elizabeth Eisenhauer for some slides!

Learning Objectives

At the end of the session the participant should be able to

- Define the objectives of “screening” vs. “definitive” trials
- Describe the possible endpoints for phase II screening trials
- Understand basic concepts of phase II design including:
 - Non-randomized two-stage designs
 - H_a , H_o , alpha and beta errors in sample size determination
 - Types of randomized phase II design and their possible uses
- Understand the role of correlative studies within phase II screening trials
- Understand some of the controversial aspects of phase II designs for trials of molecular targeted agents.

Phase II Trials: Outline

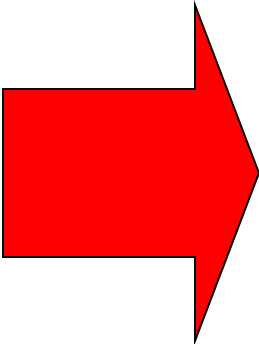
- Role of phase II trials
- Objectives
- Endpoints
- Patient Population
- Design
- Special considerations:
 - Targeted agents
 - Randomized phase II trials
 - Correlative studies

Translation: From Laboratory Hypothesis to New Therapy

PRECLINICAL

Laboratory efficacy

Preclinical toxicology



CLINICAL

Dose determination
Pharmacokinetics



Preliminary
clinical efficacy



Definitive
assessment of
efficacy

TRIAL

I

II

III

Trial Examples

Erlotinib

- EGFR tyrosine kinase inhibitor
- Oral phase I trial:
 - 150 mg po daily tolerable
 - toxicities: rash, diarrhea
- Question:
 - Does it show activity in ovarian cancer, a disease with high frequency of EGFR overexpression?

CCI-779

- mTOR inhibitor: theoretically of interest when PTEN loss
- IV phase I trial:
 - 25 mg IV weekly tolerable
 - toxicities : rash, mucositis
- Question:
 - Does it show activity in endometrial cancer, a disease with high frequency of PTEN mutation?

To Demonstrate Efficacy

- Screening trials – *does agent merit more study?*
 - Phase II studies
 - “Intermediate” endpoints (e.g. objective response)
- Definitive trials – *should this agent be adopted into practice?*
 - Phase III studies
 - Definitive, clinically meaningful endpoints (e.g. survival)

Objectives of Phase II Trials

- Primary:
 - To estimate level of **anti-tumour activity** of an agent or regimen in a given tumour type
- Secondary
 - To provide (further) information on **toxicity**
 - If applicable and possible, to generate hypotheses about relationship of **features of drug target** in tumours and response (or progression).

What are features of optimal *endpoint* for a *screening* trial?

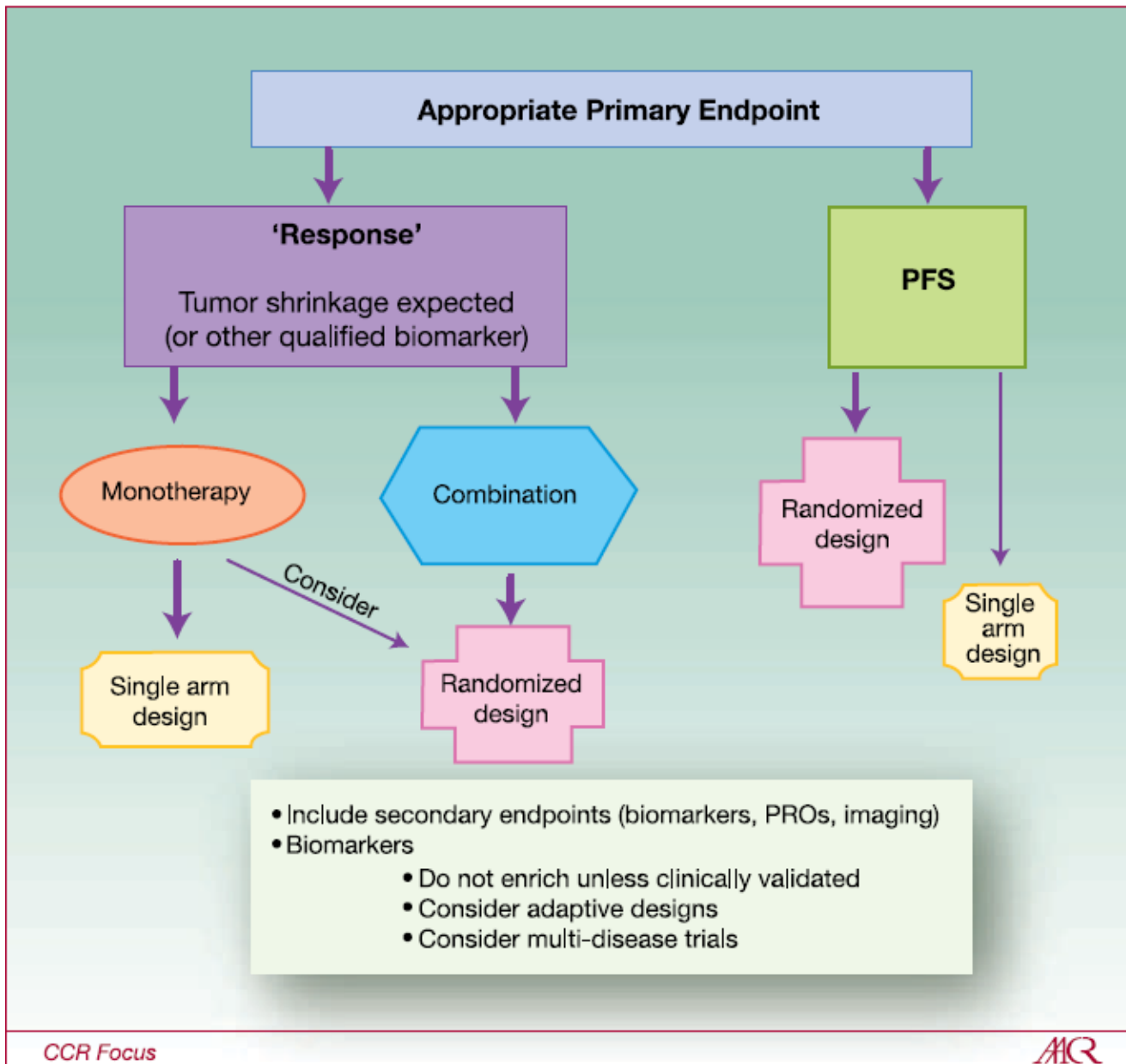
1. Measures an effect on tumour
2. Standard definition of “effect”
3. Unlikely seen as part of natural history
4. Relatively early event
5. Experience shows *it can reliably identify drugs active in phase III*

CCR FOCUS

The Design of Phase II Clinical Trials Testing Cancer Therapeutics: Consensus Recommendations from the Clinical Trial Design Task Force of the National Cancer Institute Investigational Drug Steering Committee

Lesley Seymour¹, S. Percy Ivy², Daniel Sargent³, David Spriggs⁴, Laurence Baker⁵, Larry Rubinstein², Mark J. Ratain⁶, Michael Le Blanc⁷, David Stewart⁸, John Crowley⁷, Susan Groshen⁹, Jeffrey S. Humphrey¹⁰, Pamela West¹¹, and Donald Berry⁸

Clin Cancer Res; 16(6) March 15, 2011



Phase II endpoints: Options

1. Objective response (e.g. RECIST)
2. Minor response
3. Proportion non-progressive (non-PD rate)
4. Progression free survival
5. Tumour marker
6. Other biomarker
7. Functional Imaging
8. Some measure of “area under the curve” of maximal % change in tumour size.

Traditional Phase II endpoint: Objective Response

- Using this endpoint in *single agent* trials:
 - Does not require randomized design (since tumour shrinkage only rarely spontaneous)
 - Has been reasonably successful in identifying drugs that can improve survival

Standard Response Criteria

Varies by tumour type. Examples:

- ***Most Solid Tumours:***
 - Objective response (e.g. RECIST 1.1)
- ***Some Solid Tumours:***
 - CA125 response (Ovarian cancer)
 - PSA response (Prostate cancer)
 - MacDonald Criteria (Brain tumours)
- **Hematological malignancies:**
 - Lymphoma
 - IWG AML criteria

RECIST version 1.1

(Response Evaluation Criteria in Solid Tumors)

EUROPEAN JOURNAL OF CANCER 45 (2009) 228–247



available at www.sciencedirect.com



journal homepage: www.ejconline.com



New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)

E.A. Eisenhauer^{a,*}, P. Therasse^b, J. Bogaerts^c, L.H. Schwartz^d, D. Sargent^e, R. Ford^f,
J. Dancey^g, S. Arbuck^h, S. Gwytherⁱ, M. Mooney^g, L. Rubinstein^g, L. Shankar^g, L. Dodd^g,
R. Kaplan^j, D. Lacombe^c, J. Verweij^k

RECIST 1.1: Measuring Disease

- Measurable lesion:
 - ≥ 10 mm longest diameter on CT scan (assuming slice thickness 5 mm)
 - ≥ 15 mm shortest diameter for lymph node
- Up to 5 largest measurable lesions assessed (maximum 2 per organ site)
- Sum of diameters

RECIST 1.1: Defining Response

- Complete Response (CR):
 - Disappearance of all disease
- Partial Response (PR)
 - **> 30% decrease in sum of diameters**
- Progression (PD)
 - **> 20% increase in sum of diameters and at least 5 mm absolute increase**
- Stable disease (SD)
 - Neither PD nor PR.
- CR, PR must be confirmed *if response primary endpoint*.
SD has protocol defined “minimum” duration

Example of Marker Response: CA125 Response

- **Gynecologic Cancer Intergroup criteria*:**
 - Patient must have one baseline elevated sample (at least 2x ULN)
 - CA125 response if:
 - **50% fall from baseline**
 - **Confirmed by repeat sample at least 28 days later**

Patient Population

- Patients to be enrolled in phase II trial should have characteristics which:
 - Allow assessment of primary endpoint in patients with disease of interest
 - Maximize the chance of seeing activity
 - Take into account drug toxicity and pharmacology

Examples: Population

CCI-779: Endometrium

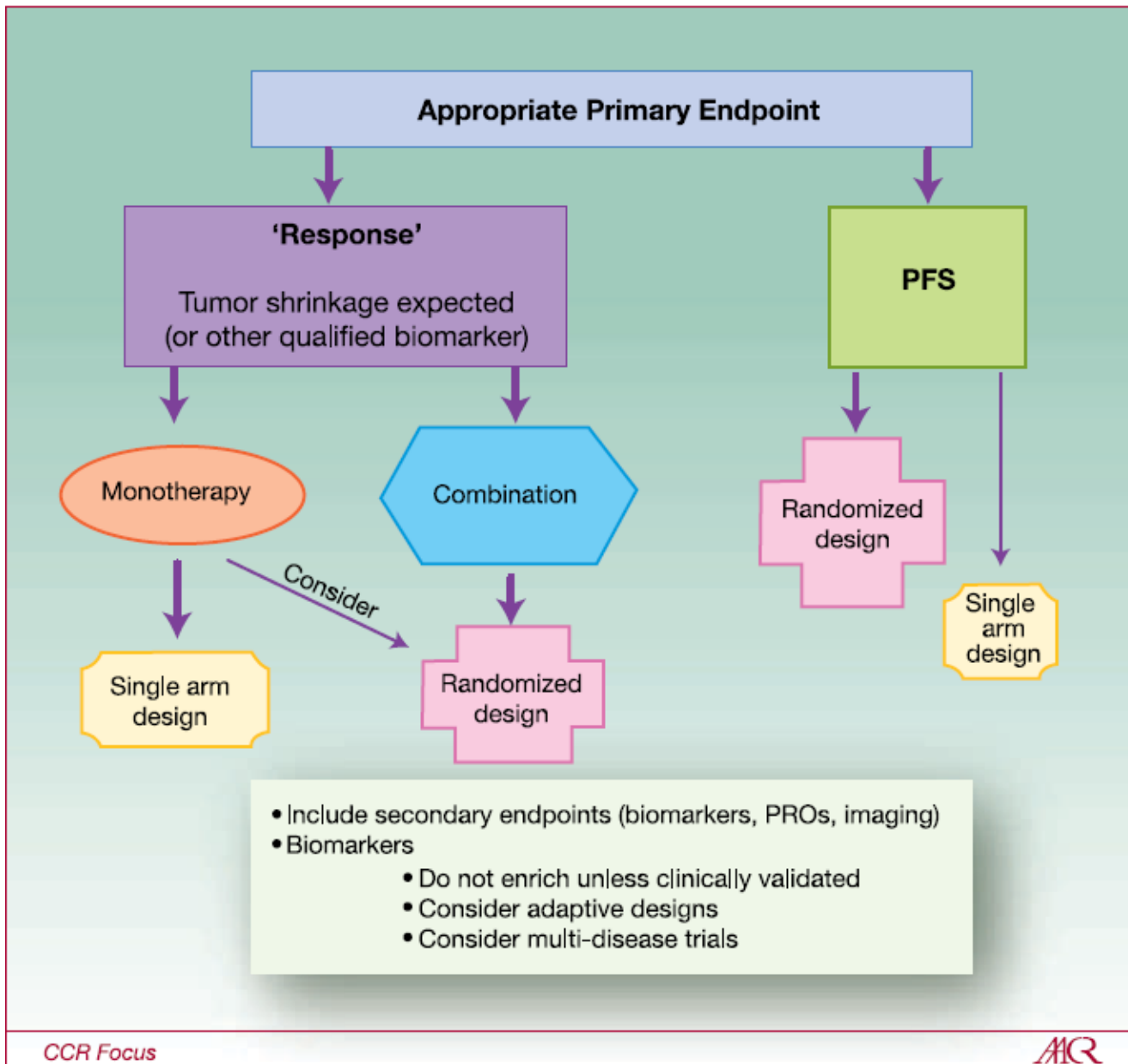
- Measurable disease
- Performance status (ECOG) 0,1,2.
- No prior chemotherapy. One hormonal treatment allowed.

Erlotinib: Ovary

- Measurable disease; +/- CA125 > 2x ULN
- Able to swallow; no bowel obstruction
- One prior chemo regimen. Two cohorts will be studied:
 - > 6 mo
 - < 6 mo

Design

- **Design should do two things:**
 - Allow identification of truly active drug (i.e. limit the risk of a false negative result)
 - Limit the number of patients treated in case the drug is truly inactive.



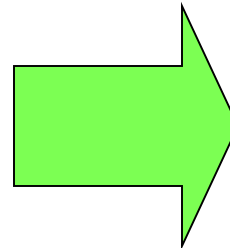
“Classic” Single Arm Design

- Multistage (usually 2-stage) non-randomized study.
- Sample size and stopping rule based on the level of activity (response rate) of interest (**Ha**) and the levels of the 2 key error rates:
 - The **α error**: false positive result
 - The **β error**: false negative result --- mostly we want to *minimize* this.

Statistical Design/Sample Size

- Several methods available:
 - Simon, Fleming, Gehan....
- **Consult with statistician**
- In general:

Smaller:
Response rate (Ha)
 α value
 β value



Larger:
Sample Size

Examples: Design

CCI-779: Endometrium

Ha 20%

Ho 5%

Enter **15** patients

- Close trial if no responses
- If ≥ 1 response: enroll 15 additional pts

If $\geq 4 / 30$ pts respond
conclude agent is of
interest for further study

$\alpha = 0.058$; $1 - \beta = 0.87$

Erlotinib: Pt. Sens. Ovary

Ha 30%

Ho 5%

Enter **8** patients

- Close trial if no responses
- If ≥ 1 response: enroll 7 additional pts

If $\geq 3 / 15$ pts respond conclude
agent is of interest for further
study

$\alpha = 0.03$; $1 - \beta = 0.85$

Platinum resistant: as at left

After Phase II is Complete:

- If a minimum level of activity seen further evaluation warranted:
 - Confirmatory phase II
 - Combination phase I/II – may be randomized
 - Randomized single agent studies
- If no responses, drug concluded to be of no interest for further study

Phase II Trials: Outline

- Role of phase II trials
- Objectives
- Endpoints
- Patient Population
- Design
- Special considerations:
 - Targeted agents
 - Randomized phase II trials
 - Correlative studies

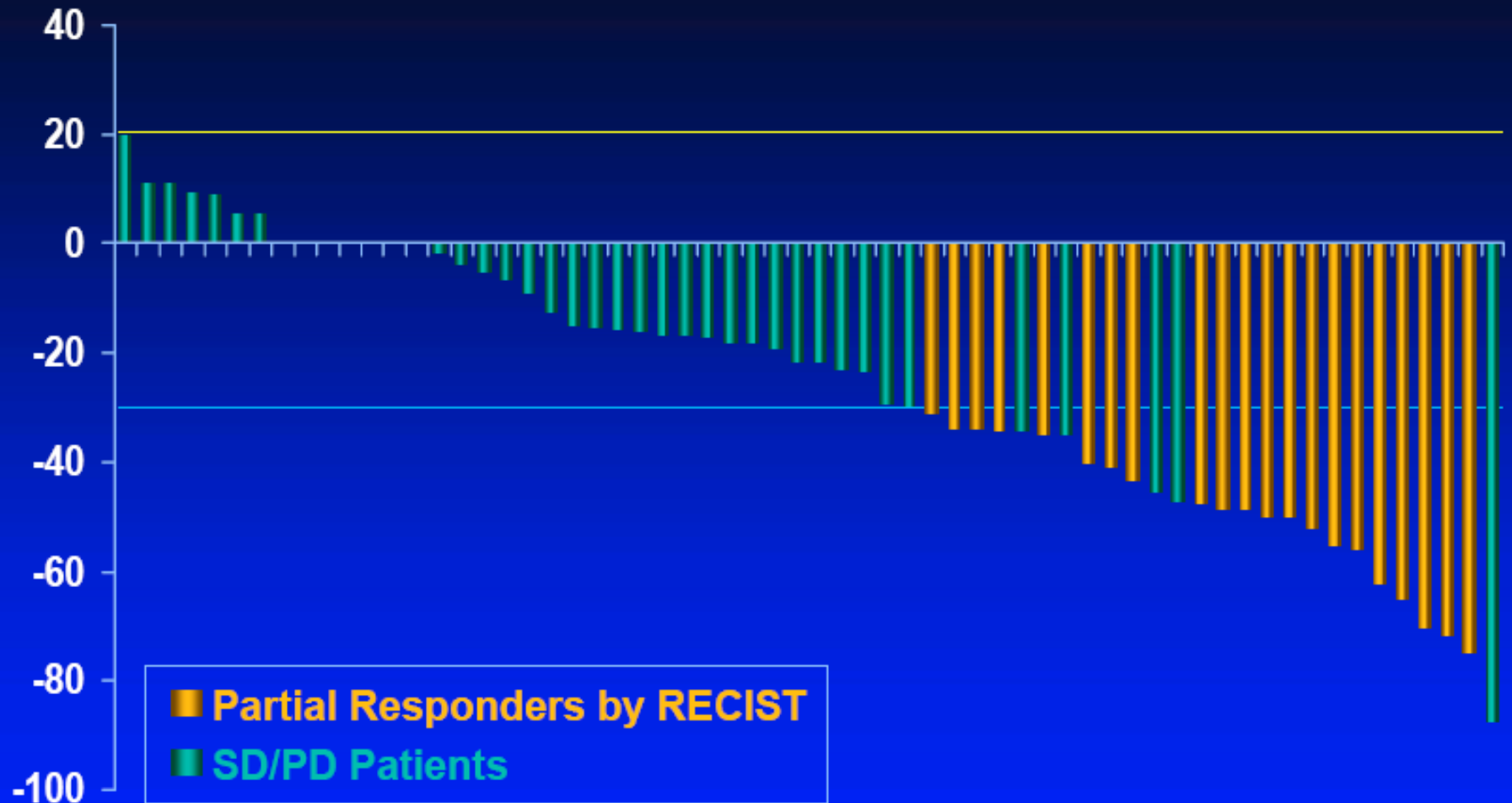
Targeted agents –Endpoint?

- Targeted anti-cancer drugs may not cause tumour shrinkage in animals
- Is response in clinical setting a realistic expectation? If not:
 - What are options for alternative endpoints?
 - What implications do use of non-response endpoints have on design?

Phase II endpoints: Options

1. Objective response (e.g. RECIST)
2. Minor response
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8. Some measure of “area under the curve” of maximal % change in tumour size.

SU11248 Maximum % Reduction of Target Lesions by Patient



Phase II endpoints:

Options

**Require
randomized
designs**

1. Objective response (e.g. RECIST)
2. Minor response
3. Proportion non-progressive (non-PD rate)
4. Progression free survival
5. Tumour marker
6. Other biomarker
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8. Some measure of “area under the curve” of maximal % change in tumour size.

What alternative endpoints/designs have been used in Phase II screening trials of targeted agents?

Agents/Targets: Phase II Review: 89 trials of 19 targeted agents

Target	Agent	#Reports
Angiogenesis	ZD6474	1
	SU5416	2
	Bevacizumab	2
	SU11248	2
PKC alpha	ISIS 3521	5
raf kinase	BAY 43-9006	1
	ISIS 5132	4
DNA MTase	MG98	1
MEK	CI-1040	1
mTOR	CCI-779	3

Target	Agent	#Reports
EGFR/ HER2	ZD1839	14
	OSI-774	5
	C225	3
	trastuzumab	8
ckit/abl	STI571	7
MMP	Marimastat	1
	BMS-275291	1
Farnesyl trans- ferase	R115777	5
	SCH66336	1

Results: Study Outcomes by Trial

Tumour Type	Number of trials with objective response rate as shown (%)				
	Not reported	0	>0 - ≤10	>10-≤20	>20
Breast	0	6	5	7	3
Colorectal	0	8	3	0	0
Lung	2	10	4	3	3
Ovary	0	3	3	0	0
Prostate	7	7	0	0	0
Renal	4	4	4	1	2
TOTAL (%)	13 (15)	38 (43)	19 (21)	11 (12)	8 (9)

Summary and Comparison of Cytotoxics with Targeted Agents Reviewed

Response rates (all trials)	No. Targeted Agents	No. Approved for ANY Tumour type Included in Review	%
10 - <20	3	2 (3)	67
>20	1	1	100
TOTAL	19	7 (8)	32

Take home message:
Objective response still useful endpoint for many “targeted agents” phase II trials.

p = .005

Randomized Phase II Designs

- Small sample size trials which are not adequately powered to compare outcomes.
- Endpoints can be response or other (e.g. PFS) depending on design and question being addressed
- Useful in several circumstances....

Examples:

Randomized Phase II Designs

- “Pick the Winner” Two schedules of a new drug look interesting. Randomized trial to select the schedule most likely to be best:
e.g. IND.163

Patients:
Breast cancer
1 prior chemotherapy



RAD001 daily

RAD001 weekly

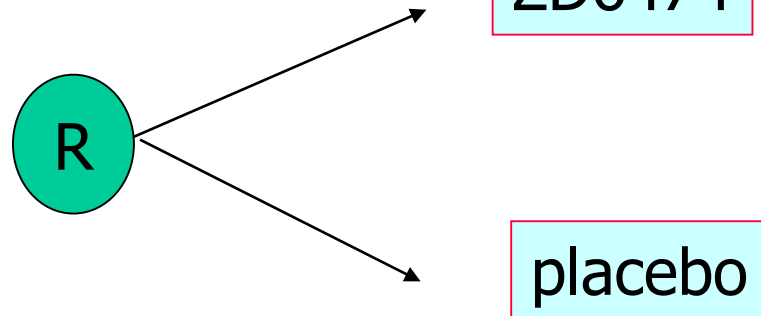
Examples:

Randomized Phase II Designs

- Identify early evidence of effect: Standard vs. experimental regimen to identify sufficient activity to merit phase III.

e.g. BR.20

Patients:
SCLC, Completed Rx
with CR, PR



Examples:

Randomized Phase II Designs

- Use control arm to interpret results:
Control arm serves to help *interpretation of results* in experimental arm
e.g. IND.165

Patients:
CRPC
No prior chemotherapy



OGX011
Docetaxel

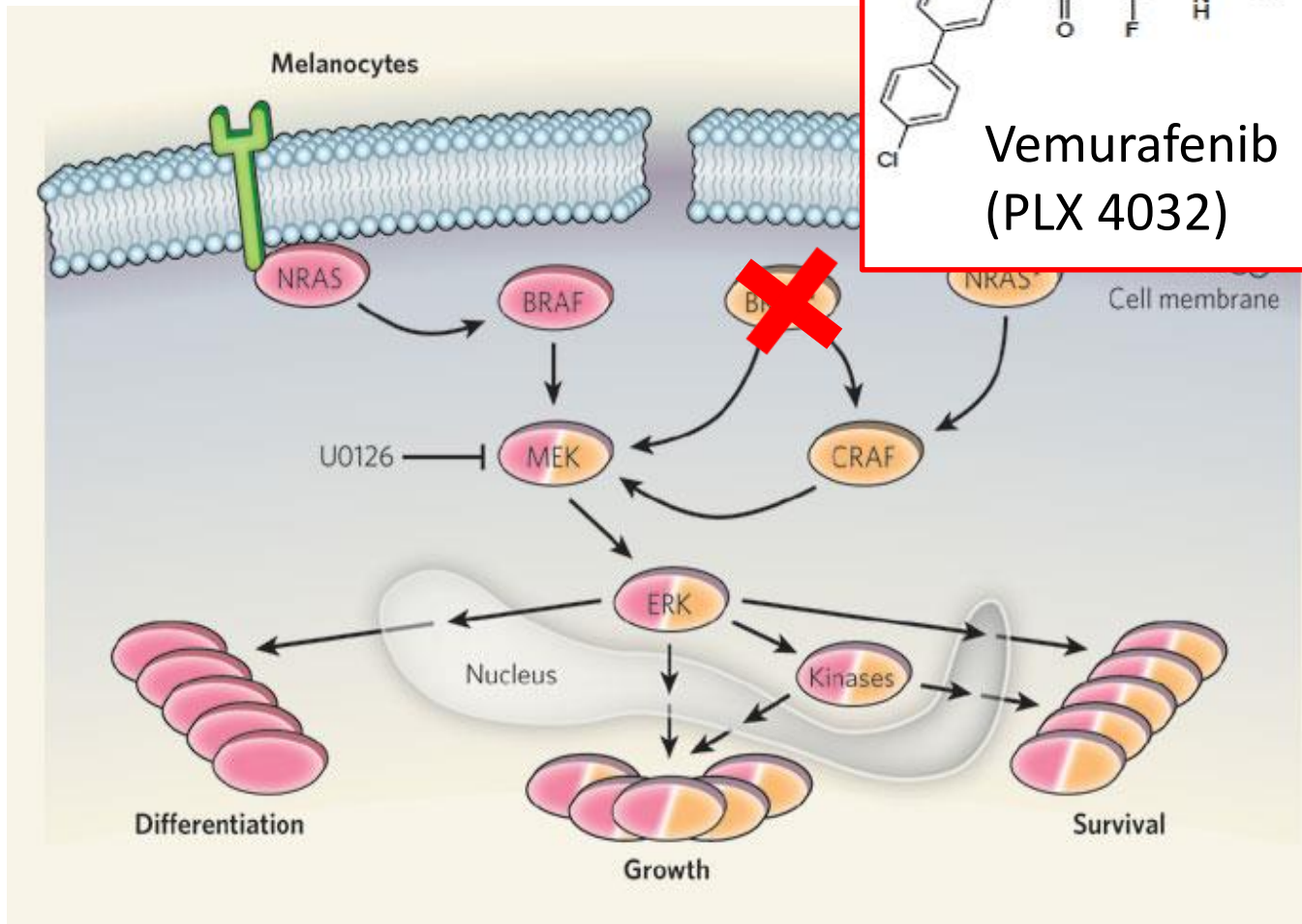
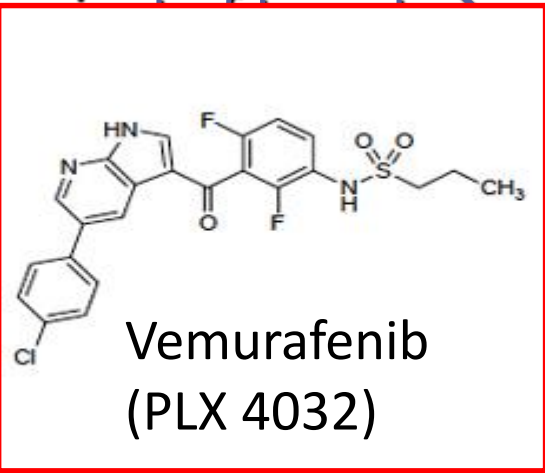
Docetaxel

Correlative Biology/Enrichment

- When to enrich for molecularly defined subset?
- What to enrich for?
- *Depends on how robust the preclinical data is on molecular predictor*
- *In all cases: need tumour collection from all patients*

An Easy Example

- Agent designed to inhibit *mutated* ... select for patients having tumours with m...



More Common Setting

- Agent affects *normal variant* of target(s)
- Most drugs affect several targets
- Phase II trial: opportunity to develop/refine *hypotheses* about which tumour subsets are most sensitive (or least insensitive)
- May be challenging – look for altered expression, mutations, amplifications in pathway and in salvage pathway

Example: Mutational Analysis in Endometrial Trial of mTOR inhibitor -- drawing a blank?

Best Response Association Tested	Mutation type	P-value
PR vs. other	Any	1.0
	PIK3CA	0.4
	PIK3CA or Akt	1.0
PR + SD vs. other	Any	0.3
	PIK3CA	0.4
	PIK3CA or Akt	0.7
PD vs. other	Any	0.7
	PIK3CA	0.7
	PIK3CA or Akt	0.7

Lesson: It is challenging to find “THE” biomarker

- Phase II can be place to start but seldom where the story finishes
- Sample size is relatively small to do much more than generate/refine hypotheses

Summary: Phase II Trials

- Goal: Screen new agent/combination for activity.
- Primary Endpoints:
 - Single agent/single arm: Objective response
 - Randomized (single agent or combo): response or PFS
- Design:
 - Depends if single arm or randomized
 - Should minimize possibility of false negative outcome
- Correlative studies: Should be routine
 - At minimum: to generate hypotheses about selection biomarker

Drugs active in phase II: Need further evaluation

Backups

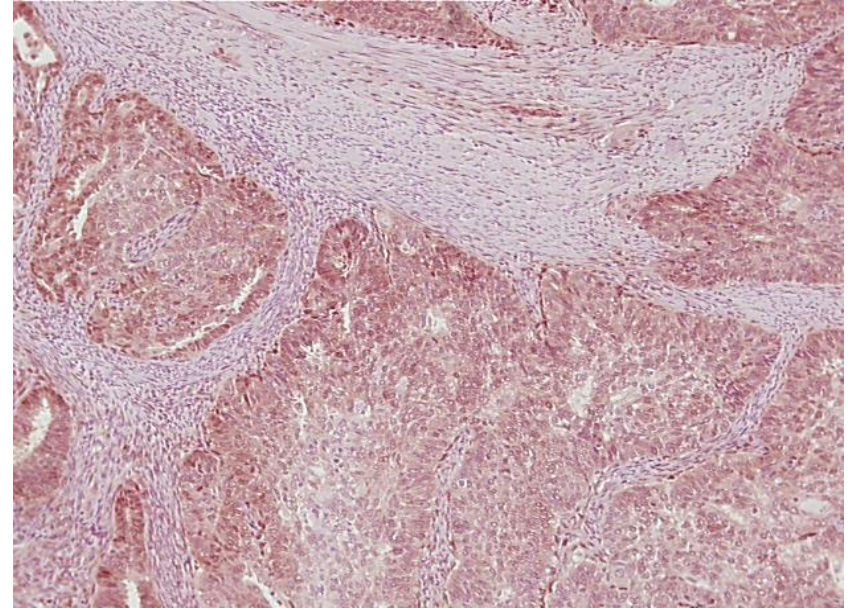
Reporting Results

- Account for all patients entered
- Describe:
 - Patient characteristics
 - Treatment delivery
 - Toxic effects
 - No. pts with: CR, PR, SD, PD
 - Response rate: based on all eligible patients (do not inflate response rate by reducing denominator)
 - Response Duration
 - Outcome of any “special” endpoint e.g. molecular marker

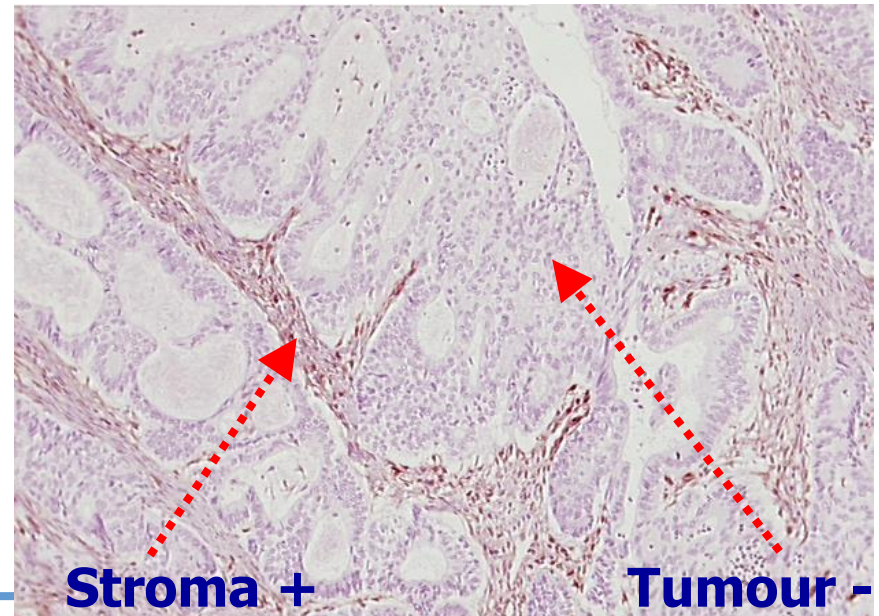
Example:

**Phase II Single Agent
Trial
mTOR inhibitor
in Endometrial ca**

PTEN IHC positive = normal



Negative = loss of PTEN expression



IND.160 A

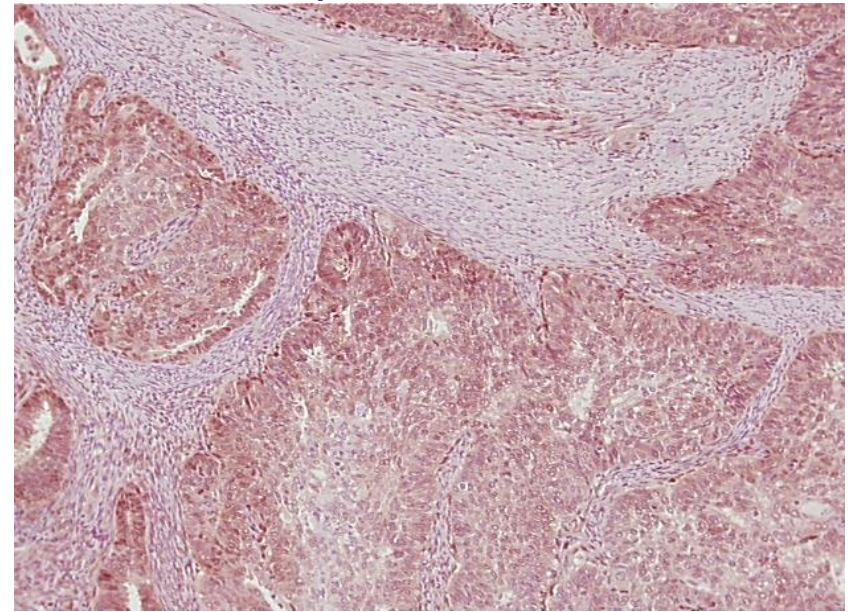
(Temsirolimus Endometrium)

Response	PTEN +ve	PTEN -ve
PR	3	1
SD	3	14
PD	3	2
IN		3
Total	9	20

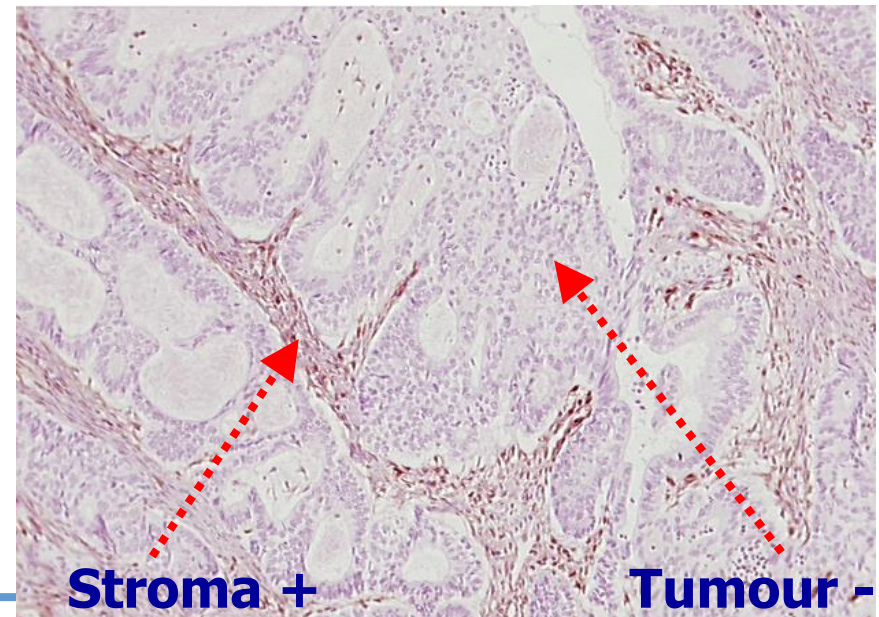
No evidence PTEN loss
needed for PR

Similar results pmTOR, pS6k

PTEN IHC positive = normal



Negative = loss of PTEN expression



Stroma +

Tumour -

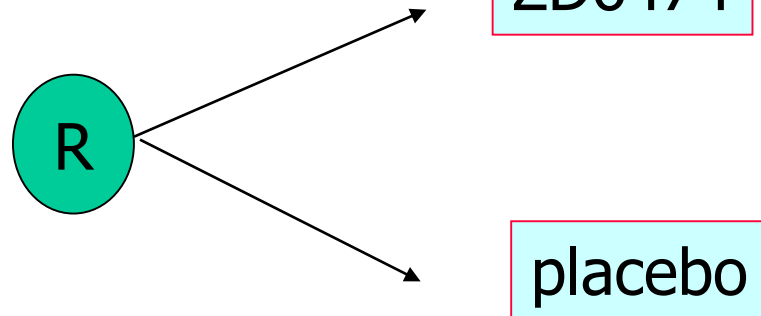
Examples:

Randomized Phase II Designs

- Identify early evidence of effect: Standard vs. experimental regimen to identify sufficient activity to merit phase III.

e.g. BR.20

Patients:
SCLC, Completed Rx
with CR, PR



Primary endpoint: 2.5 mo improvement in PFS
Statistics: power 80%, one-sided alpha 0.1

Examples:

Randomized Phase II Designs

- Use control arm to interpret results:
Control arm serves to help *interpretation of results* in experimental arm
e.g. IND.165

Patients:
CRPC
No prior chemotherapy



OGX011
Docetaxel

Docetaxel

Primary endpoint: PSA response rate

Statistics:

- $H_0 < 40\%$, $H_1 > 60\%$, $\alpha = 0.1$, $\beta = 0.1$
- $>20/40$ pts in OGX-011 Arm with PSA resp of interest

What alternative endpoints/designs have been used in Phase II screening trials of targeted agents?

- 19 targeted agents with single agent phase II reports in one of 6 common tumour types
- Describe endpoints, design used and whether results related to eventual phase III success
- Total: **89 trials found**

Era of Molecular Targeted Therapy: Phase II Trial Challenges

- Is response a realistic endpoint with molecular targeted agents?
- If not:
 - What are options of alternative endpoints?
 - What implications do use of non-response endpoints have on design?
- Should population be “enriched” for target expression?