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
  – $H_0$, $H_a$, 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
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
Appropriate Primary Endpoint

‘Response’
Tumor shrinkage expected (or other qualified biomarker)

- Monotherapy
  - Single arm design
- Combination
  - Randomized design

PFS

Randomized design
- Single arm design

Include secondary endpoints (biomarkers, PROs, imaging)
- Biomarkers
  - Do not enrich unless clinically validated
  - Consider adaptive designs
  - Consider multi-disease trials
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
New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1)

E.A. Eisenhauer\textsuperscript{a,*}, P. Therasse\textsuperscript{b}, J. Bogaerts\textsuperscript{c}, L.H. Schwartz\textsuperscript{d}, D. Sargent\textsuperscript{e}, R. Ford\textsuperscript{f}, J. Dancey\textsuperscript{g}, S. Arbuck\textsuperscript{h}, S. Gwyther\textsuperscript{i}, M. Mooney\textsuperscript{g}, L. Rubinstein\textsuperscript{g}, L. Shankar\textsuperscript{g}, L. Dodd\textsuperscript{g}, R. Kaplan\textsuperscript{j}, D. Lacombe\textsuperscript{c}, J. Verweij\textsuperscript{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**.
Appropriate Primary Endpoint

'Response'
Tumor shrinkage expected (or other qualified biomarker)

Monotherapy
Consider
Single arm design

Combination
Randomized design

PFS
Randomized design
Single arm design

- Include secondary endpoints (biomarkers, PROs, imaging)
- Biomarkers
  - Do not enrich unless clinically validated
  - Consider adaptive designs
  - Consider multi-disease trials
“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 $\alpha$ error: false positive result
  – The $\beta$ 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)
  - $\alpha$ value
  - $\beta$ 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 ≥ 4/30 pts respond conclude agent is of interest for further study
α = 0.058; 1 - β = 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 ≥ 3/15 pts respond conclude agent is of interest for further study
α = 0.03; 1 - β = 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
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.
SU11248 Maximum % Reduction of Target Lesions by Patient

- Partial Responders by RECIST
- SD/PD Patients
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.
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

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>#Reports</th>
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<tbody>
<tr>
<td>Angiogenesis</td>
<td>ZD6474</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>SU5416</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Bevacizumab</td>
<td>2</td>
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<td></td>
<td>SU11248</td>
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<tr>
<td>PKC alpha</td>
<td>ISIS 3521</td>
<td>5</td>
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<tr>
<td>raf kinase</td>
<td>BAY 43-9006</td>
<td>1</td>
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<td></td>
<td>ISIS 5132</td>
<td>4</td>
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<td>DNA MTase</td>
<td>MG98</td>
<td>1</td>
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<tr>
<td>MEK</td>
<td>CI-1040</td>
<td>1</td>
</tr>
<tr>
<td>mTOR</td>
<td>CCI-779</td>
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<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
<th>#Reports</th>
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<td>EGFR/HER2</td>
<td>ZD1839</td>
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<td></td>
<td>OSI-774</td>
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<td></td>
<td>C225</td>
<td>3</td>
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<td></td>
<td>trastuzumab</td>
<td>8</td>
</tr>
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<td>ckit/abl</td>
<td>STI571</td>
<td>7</td>
</tr>
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<td>MMP</td>
<td>Marimastat</td>
<td>1</td>
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<tr>
<td></td>
<td>BMS-275291</td>
<td>1</td>
</tr>
<tr>
<td>Farnesyl transferase</td>
<td>R115777</td>
<td>5</td>
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<tr>
<td></td>
<td>SCH66336</td>
<td>1</td>
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</table>

*El-Maraghi, Eisenhauer, JCO, 2008*
## Results: Study Outcomes by Trial

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Not reported</th>
<th>0</th>
<th>&gt;0 - ≤10</th>
<th>&gt;10-≤20</th>
<th>&gt;20</th>
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<tr>
<td>Breast</td>
<td>0</td>
<td>6</td>
<td>5</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Colorectal</td>
<td>0</td>
<td>8</td>
<td>3</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Lung</td>
<td>2</td>
<td>10</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Ovary</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Prostate</td>
<td>7</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Renal</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>TOTAL (%)</strong></td>
<td><strong>13 (15)</strong></td>
<td><strong>38 (43)</strong></td>
<td><strong>19 (21)</strong></td>
<td><strong>11 (12)</strong></td>
<td><strong>8 (9)</strong></td>
</tr>
</tbody>
</table>
# Summary and Comparison of Cytotoxics with Targeted Agents Reviewed

<table>
<thead>
<tr>
<th>Response rates (all trials)</th>
<th>No. Targeted Agents</th>
<th>No. Approved for ANY Tumour type Included in Review</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 - &lt;20</td>
<td>3</td>
<td>2 (3)</td>
<td>67</td>
</tr>
<tr>
<td>&gt;20</td>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>TOTAL</td>
<td>19</td>
<td>7 (8)</td>
<td>32</td>
</tr>
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</table>

**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

R

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

R

- ZD6474
- placebo
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

```
R
```

```
OGX011
Docetaxel
```

```
Docetaxel
```

```
Patients: CRPC No prior chemotherapy
```
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 variant of target. Select for patients having tumours with mutated target.

Vemurafenib (PLX 4032)
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?

<table>
<thead>
<tr>
<th>Best Response Association Tested</th>
<th>Mutation type</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR vs. other</td>
<td>Any</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>PIK3CA</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>PIK3CA or Akt</td>
<td>1.0</td>
</tr>
<tr>
<td>PR + SD vs. other</td>
<td>Any</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>PIK3CA</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>PIK3CA or Akt</td>
<td>0.7</td>
</tr>
<tr>
<td>PD vs. other</td>
<td>Any</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>PIK3CA</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>PIK3CA or Akt</td>
<td>0.7</td>
</tr>
</tbody>
</table>
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

Stroma +

Tumour -
**IND.160 A**

*(Temsirilimus Endometrium)*

<table>
<thead>
<tr>
<th>Response</th>
<th>PTEN +ve</th>
<th>PTEN -ve</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>SD</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>PD</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>IN</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>20</td>
</tr>
</tbody>
</table>

PTEN IHC positive = normal

Negative = loss of PTEN expression

No evidence PTEN loss needed for PR

Similar results pmTOR, pS6k

NCIC CTG

GEC NCIC
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

  - ZD6474
  - placebo
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

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

OGX011 Docetaxel
Docetaxel
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

El-Maraghi, Eisenhauer, JCO, 2008
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?