Panel Four:

Development Paths for New Drugs with Large Treatment Effects Seen Early
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
Development Paths for New Drugs with Large Treatment Effects Seen Early

Jane Perlmutter
Patient Advocate
janep@gemini-grp.com
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

<table>
<thead>
<tr>
<th>When Appropriate</th>
<th>Accelerated Approval</th>
<th>Potential New Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Significant early effects for diseases with limited other options</td>
<td>• Unusually large effects in early trials</td>
</tr>
</tbody>
</table>

| Pros | • Make potentially useful new agents rapidly available to patients with limited options | • Make potentially useful new agents rapidly available to patients with limited options |
|      | • Provide early opportunity for developers to receive reimbursements | • Provide early opportunity for developers to receive reimbursements |
|      | • Provide additional assessment of safety (including late occurring toxicities) and efficacy | • 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**
- Ethical and practical issues accruing patients to randomized trials once new agents become available
- Increasingly small populations
- Difficulty dealing with multiple outcomes

**Potential Solution**
- Unbalanced and/or adaptive randomization designs; registration trials
- Decision Analysis
- Bayesian Approaches
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

What magnitude and what duration is needed?

Intervention

Molecular Target

Clinically Meaningful Endpoint *

Disease

* 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
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)
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:**
  
  ~ \( \frac{1}{4} \) the size of a stand alone registrational Phase 3 trial (i.e., \( \frac{1}{4} \) of an SOE2 trial)

- **120 events (approx. 451 * .25)**
Outcome Probabilities — Phase 2b Trial Design, (120 events)

Outcome Probabilities — Phase 3 Trial Design, (451 events)
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. $\Delta = 3.2$ 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

- 5-FU+LEV n=91
- Levamisole n=85
- Control n=86

Surviving, %
0 10 20 30 40 50 60 70 80 90 100

Years from randomization
Outcome Probabilities — Phase 2b Trial Design, (120 events)

Outcome Probabilities — Phase 3 Trial Design, (451 events)
SURGICAL ADJUVANT THERAPY OF COLORECTAL CANCER

NCCTG Trial

Surviving, %

Years from randomization

- 5-FU+LEV n=91
- Levamisole n=85
- Control n=86

Cancer Intergroup Trial
SURGICAL ADJUVANT THERAPY OF COLORECTAL CANCER

NCCTG Trial

Cancer Intergroup Trial

Surviving, %

Years from randomization

Surviving, %

Years from randomization

5-FU+LEV n=91
Levamisole n=85
Control n=86

5-FU+LEV n=304
Levamisole n=310
Control n=315
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?

~ Phase 2b: (Randomized Screening Trial)
  …if true effect is *moderate*

~ Phase 3: (Randomized Registration Trial)
  …if true effect is *very large*
Outcome Probabilities — Phase 2b Trial Design, (120 events)

\[ \Delta \text{ in months} \quad 0 \quad 1.3 \quad 2.6 \quad 3.2 \quad 5.0 \]

Add’l trials  Positive

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

\[ \Delta \text{ in months} \quad 0 \quad 2.0 \quad 3.2 \]

Positive
Illustration of a Phase 2b Trial with “Compelling” Results: HIVNET 012

- Results  

Lancet 1999; 354: 795-802

<table>
<thead>
<tr>
<th></th>
<th>MCT of HIV</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>6-8 wks</td>
<td>14-16 wks</td>
</tr>
<tr>
<td>AZT</td>
<td>302</td>
<td>59 (21.3%)</td>
<td>65 (25.1%)</td>
</tr>
<tr>
<td>NVP</td>
<td>307</td>
<td>35 (11.9%)</td>
<td>37 (13.1%)</td>
</tr>
</tbody>
</table>

1p = 0.0014  
1p = 0.0003
Outcome Probabilities — Phase 2b Trial Design, (102 events)

% Relative Risk ↓ 0 18 30 35 45

Add’l trials Positive

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

% Relative Risk ↓ 0 26 35

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

% Relative Risk ↓ 0 18 30 35 45

Paclitaxel

Capecitabine

* *

PFS: Sorafenib in Breast Cancer

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

% Relative Risk ↓ 0 26 35

Positive

Add’l trials

Positive
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
Conference on Clinical Cancer Research

Development Paths for New Drugs with Large Treatment Effects Seen Early

Janet Woodcock
FDA

November 10, 2011 • Washington, DC
2011 Conference on Clinical Cancer Research

Case studies/Industry Perspective
Gracie Lieberman
November 10, 2011
Vemurafenib in V600E BRAF Melanoma

Early signal of activity (n=16)
- Phase I response rates: 69%
- Historical response rates: 10-20%

Randomized phase 3: Vemurafenib vs. standard of care
- OS primary endpoint per HA; targeted HR: 0.75
- 80% power and two-sided 2.5% level of significance
- 680 patients (468 events planned)

August 2009
- Phase 2 response rates: 52% (n=132)

October 2010; Phase 3 amendment per HA
- Overall alpha level increased to 2-sided 5% from 2-sided 2.5%
- Alpha spending rule set with higher probability to cross at IA
- Less conservative target HR: 0.65
- PFS added as a co-primary endpoint
- Criteria for cross-over established

August 2011
- Full approval based on positive final PFS and interim OS analysis
  - PFS HR: 0.26; 95% CI: (0.20, 0.33)
  - OS HR: 0.44; 95% CI: (0.33, 0.59)
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

Complete Response
- Additional Study to Confirm Durable Response/ Cure
  - Full Approval

Partial Response
- Single Arm Phase II
  - AA* or Full Approval
- Randomized Phase II
  - Full Approval
- Traditional Path Phase II/III
  - Full Approval

* May or may not require randomized confirmatory study
Industry Considerations for Development Paths

Large treatment effects observed early

Complete Response

- Additional Study to Confirm Durable Response/ Cure
- Full Approval

Partial Response

- Single Arm Phase II
  - AA* or Full Approval
- Randomized Phase II
  - Full Approval
- Traditional Path Phase II/III
  - Full Approval

- Rate of complete response
- Confirmation of response
- Duration of response
Industry Considerations for Development Paths

Large treatment effects observed early

Complete Response
- Additional Study to Confirm Durable Response/ Cure
  - Full Approval

Partial Response
- Single Arm Phase II
  - AA* or Full Approval
- Randomized Phase II
  - Full Approval
- Traditional Path Phase II/III
  - Full Approval

- 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

Complete Response
- Additional Study to Confirm Durable Response/ Cure
  - Full Approval

Partial Response
- Single Arm Phase II
  - AA* or Full Approval
- Randomized Phase II
  - Full Approval

Traditional Path Phase II/III
- Full Approval
Industry Considerations for Development Paths

Large treatment effects observed early

Complete Response
- Additional Study to Confirm Durable Response/ Cure
  - Full Approval

Partial Response
- Single Arm Phase II
  - AA* or Full Approval
- Randomized Phase II
  - Full Approval
- Traditional Path Phase II/III
  - Full Approval

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?
Development Paths for New Drugs with Large Treatment Effects Seen Early

Wyndham Wilson
NCI

November 10, 2011 • Washington, DC
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
Conference on Clinical Cancer Research

Development Paths for New Drugs with Large Treatment Effects Seen Early

Edward Korn
NCI

November 10, 2011 • Washington, DC
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 benefit:risk evaluation

• Large effect is a moving target

• Consult FDA if large effect is observed in early development for future design of studies