Development of Two Novel Therapeutics Targeting Multiple Pathways

C. Erlichman
Professor of Oncology
Mayo Clinic
Current State of Oncology Drug Development¹

- Strong medical need for improvement in cancer treatment
- Time to submission of NDA is 1.5 years longer for oncology agents than other agents
- 32% of oncology drugs are tests in at least 4 indications compared to 9% in other therapeutic areas
- Only 1 in 5 oncology drugs entering clinical trial will attain marketing approval
CHALLENGE

• Multiple New Molecular Targets
  • Many choices
• Targets in Tumor and in Normal Tissue
  • Paradigm shift from tumor only
• Biologic
  • Cross-talk
  • Redundancy
  • Feedback
• Regulatory
  • Safety, Effectiveness, Efficiency
AR transcription may be enhanced through IGF1R activation of AR co-regulators.
• Targeting mTOR can increase Akt activation
• Simultaneous targeting of PI3K-Akt may be synergistic
• Targeting EGFR can activate another RTK (IGF1R) that signals through the same downstream transducers as EGFR

Morgillio, F. et al Drug Resist Updat. 2005;8:298
Development of Combination NMEs

• Paradigm of drug development needs to shift based on pathway and network analysis not just target

• A single agent will not be able to adequately address pathways and their interaction so combinations need to be developed

• Strategies to develop combinations so that non-productive combinations can be abandoned earlier
Questions?

• What level of scientific understanding of treatment action is enough?
• How can we develop effective therapies when single agents do not demonstrate sufficient promise to meet criteria for registration?
• How can combination drug development proceed efficiently yet safely?
• How can companies be held safe from regulatory risk for individual agents when combining 2 new medical entities (NMEs)?
Presentations

• The importance of the issue from patient’s perspective – Dr. Clark

• Synthetic lethality – Dr. Ellis

• Co-enhancement and One-way enhancement – Dr. Lutzker

• Rationale for modifying current approval policies – Dr. Zwiebel

• Reaction to panel – Dr. Woodcock
Conference on Clinical Cancer Research

Supported by:

September 14, 2009 • Washington, DC
Brookings Conference on Clinical Cancer Research

Access to Rational Drug Combinations as a Treatment Option

Adam M. Clark, Ph.D.
Director of Research and Policy
adam.clark@livestrong.org
Founded in 1997 by Lance Armstrong

- Our mission: To inspire and empower people affected by cancer
- Our Objective: Take aim at the gap between what is known and what is done
Treatment Summary

- Removal of the testicle (orchiectomy)
- Surgery involving the brain or spinal cord
- One round of BEP (Bleomycin, Etoposide and Platinol) cisplatin (platinol®)
- Three rounds of VIP chemotherapy (Ifosfamide, Etoposide and Platinol.)

Risks Associated with Tx

- 2X Risk of a second cancer
- Bladder or urinary tract toxicities
- Osteoporosis and osteopenia
- Risk of cardiac problems
- Fertility and sexuality concerns
- Elevated cholesterol levels
- Ototoxicity (hearing loss, tinnitus, vertigo)
- Peripheral neuropathy
- Lung (pulmonary) Complications
“...the one thing that I've heard the most is the tobacco issue. The second most common thing that I've heard would be clinical trials. Everybody in the field agrees that if we can enroll more people in clinical trials, we would have much greater success...”

“Let's face it: chemotherapy is chemotherapy. Ideally, in 10 or 20 or 30 years, you look at chemotherapy, and you go, Jesus Christ, did we really do that to people?”

Lance Armstrong, U.S. Senate Testimony, 2008
• 1960 Discovery of abnormal chromosome 22, the Philadelphia Chromosome in chronic myelogenous leukemia (CML) patients
• 1973 Lengthy chromosome 9 correlated with chromosome 22 deletion in CML
• 1982-87 Discovery of abl translocation and fusion with bcr
• 1996 Compound STI571 inhibits growth of BCR-ABL expressing cells
• 1999 Clinical trials for STI571
• 2001 FDA approval of Gleevec
• Total – 41 years!
• Educational Network to Advance Cancer Clinical Trials (ENACCT) co-founded by LIVESTRONG

• LIVESTRONG SurvivorCare
  – 44% of inquiries directed to EmergingMed for clinical trials matching
  – 90% of “qualified” individuals are interested in getting more information on molecular profiled clinical trials matching services

• Goal to expand education efforts on the benefits of clinical trials, particularly in ethnic and racial minorities, adolescents and young adults, and the medically underserved
• American College of Surgeons Commission on Cancer includes access to cancer clinical trials as key quality measures for delivery services

• Estimated 20% of adult cancer patients are medically eligible for a cancer clinical trial, but only 3-5% enroll

• AYA populations (15-39 yrs) have some of the lowest accrual rates and overall survival hasn’t increased in 20-30 years

• Ethnic and racial minorities also have lower accrual rates and higher cancer mortality rates than the population as a whole
• AYA tumors may have a distinctive biology compared to pediatric or adult tumors which can influence prognosis and treatment.

• Differences in race and ethnicity may also comprise genotypically variant populations with differences in response to targeted treatments.

• As our ability to molecularly profile cancers improves, access to novel drug combinations based on this biology of the cancer provides options and choices for the patient.
THE FUTURE: TAILORING MULTIPLE NEW TREATMENTS

Nature 455, 1061-1068 (23 October 2008)
• Patient safety and education about trials and treatments always should remain the top priority in choosing options
• A strong biological rationale engages the patient, the doctor, and the researcher in determining the best options
• Co-development of drugs based on biology improves access for all populations and may provide tailored options for genotypically different sub-populations
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Synthetic Lethality

Matthew J. Ellis
Professor of Medicine
Washington University in St. Louis
Synthetic lethality
From Wikipedia, the free encyclopedia

**Synthetic lethality** and **Synthetic Sickness** (collectively known as SSL) refer to a genetic interaction where two separate strains with viable mutations result in reduced or no growth when combined in a double mutant containing both.

**Nature Genetics:**
Synthetic lethality occurs when two otherwise nonlethal mutations together result in an inviable cell.

“Two defect hypothesis for cancer treatment to target the functional redundancy in living systems”
SYNTHETIC LETHAL CONTEXT 1
DNA REPAIR DEFECT

DEFECT 1: DNA REPAIR – BRCA MUTATION

DEFECT 2: IS INDUCED BY AGENTS THAT TARGET ALTERNATIVE DNA REPAIR MECHANISMS
Mechanism of Cell Death from Synthetic Lethality, as Induced by Inhibition of Poly(Adenosine Diphosphate [ADP]-Ribose) Polymerase 1 (PARP1)

EXTENSION OF CONTEXT TO TNBC

DEFECT 1: DNA REPAIR – UNCERTAIN ETOLOGY, BUT CHROMOSOME INSTABILTY PHENOTYPE CHARACTERISTIC

ENHANCE PHENOTYPE OF DNA REPAIR DEFECT USING DNA DAMAGING AGENTS TO CAUSE DNA STRAND BREAKS

DEFECT 2: IS INDUCED BY PHARMACOLOGICAL INTERVENTION THAT INHIBITS DNA REPAIR PATHWAY
Overall Survival

BSI-201 + Gem/Carbo (n = 57)
Median OS = 9.2 months

Gem/Carbo (n = 59)
Median OS = 5.7 months

$P = 0.0005$
HR = 0.348 (95% CI, 0.189-0.649)

O’Shaughnessy
ASCO 2009
SYNTHETIC LETHAL CONTEXT 2

DEFECT IN CELL DEATH IN ER+ BREAST CANCER

ESTROGEN DEPENDENT TISSUES ATROPHY IN THE PRESENCE OF NATURAL ESTROGEN DEFICIENCY (MENOPAUSE)

PI3KINASE MUTATIONS PREVENT ATROPHY OF ESTROGEN DEPENDENT ORGANS TO PRODUCE ESTROGEN DEPENDENT MALIGNANCIES
PIK3CA mutations are common in ER+ Breast cancer

About 30% of ER+ Breast Cancers have PIK3CA gain of function mutations
PI3K Pathway Signaling and Aberration in Breast Cancer
CROWDER, ELLIS ET AL CANCER RESEARCH 2009: 69, 3955
BEZ235 Induces Apoptosis in Estrogen-Deprived ER+ Cells

Cell Signaling

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<tr>
<th>Treatment</th>
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<tr>
<td>Serum</td>
<td>+ DEXO</td>
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<tr>
<td>Act</td>
<td>+ BEZ235</td>
</tr>
<tr>
<td>p-Akt</td>
<td>+ BEZ235</td>
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<tr>
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<td>+ BEZ235</td>
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<tr>
<td>p-S6</td>
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<td>P-Erk 1/2</td>
<td>+ BEZ235</td>
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<tr>
<td>Actin</td>
<td>+ BEZ235</td>
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BEZ235 IC₅₀s:
- p110α – 5 nM
- p110β – 75 nM
- mTOR – 20 nM

Cell Death

MCF-7

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<td>20</td>
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MDA-MB-231

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HCC712

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<td>-</td>
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<td>20</td>
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<td>50</td>
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T47D

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<th>BEZ235 (nM)</th>
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<tr>
<td>50</td>
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CONTEXT 2

DEFECT IN CELL DEATH

BOTH ESTROGEN AND PI3 KINASE INDEPENDENTLY PROMOTE THE SURVIVAL OF ER+ TUMORS

INHIBITION OF ESTROGEN PRODUCTION AND PI3KINASE INDUCES SYNTHETIC LETHALITY IN ESTROGEN-DEPEDEDENT ORGANS
Other Examples

- CHK1 inhibitors in TP53 mutant cancer in combination with chemotherapy.

- MTAP (salvage of both adenine and methionine) is deleted in CDK2N mutant breast cancer and may induce sensitivity to inhibitors of de novo adenine synthesis (L-alanosine)
Whole Genome Sequencing
Clinical Evaluation of 2NME Combinations for Oncology Indications

Stuart Lutzker, MD-PhD
Vice President
BioOncology Exploratory Clinical Development
Genentech Inc

Sept14th, 2009
Assumptions For a 2NME Clinical Development Plan

• Effective targeting of key parallel or compensatory pathways in cancer will likely require a combining unapproved agents given the limited number of available approved agents

• Clinical development plans should avoid exposing large number of patients to single agent NME’s that have minimal or modest activity in preclinical testing

• 2NME combo development should initiate early in clinical development with appropriate safety plans

• Regulatory path for NME approval needs to include the potential for first approval as part of a 2NME combo
Typical Clinical Development Plan for a single NME*

- Suitable PK and safety with adequate exposure?
- NME active with sufficient safety for pivotal study?
- Statistically significant clinical benefit with adequate safety?

Phase I NME

Randomized Phase II NME vs SOC

Randomized Phase III NME vs SOC

*Assumes replacement strategy vs SOC; could also be add-on strategy combining w/ SOC requiring standard Phase Ib study
Proposed Clinical Development Plan for a 2NME Combo based on Synthetic Lethality

- **Phase Ib**
  - NME A run-in
  - NME A + NME B
  - NME B run-in
  - NME A + NME B

- **Randomized Phase II**
  - NME A + NME B vs SOC

- **Randomized Phase III**
  - NME A + NME B vs SOC

---

# Assumes A and B have minimal potential for antitumor activity as single agents

* Assumes replacement strategy vs SOC; could also be add-on strategy combining w/ SOC
Proposed Clinical Development Plan for a 2NME Combo based on Co-enhancement

**Phase I NME A**

**Phase I NME B**

**Phase Ib**

NME A + NME B

**Randomized Phase II**

NME A + NME B vs NME A vs NME B vs SOC

**Randomized Phase III**

NME A + NME B vs SOC

---

# Assumes A and B have modest potential for antitumor activity as single agents

* Assumes replacement strategy vs SOC; could also be add-on strategy combining w/ SOC

Suitable PK, safety and TI?

Safety with adequate exposure?

Combo active with adequate safety for pivotal study and activity unlikely to be due to single agent NME?

Statistically significant clinical benefit with adequate safety?
2NME Phase Ib Co-enhancement Dose Escalation Schema

- Dose escalate each NME in parallel to MTD (see example)
- Alternatively hold one NME constant while dose escalating other NME to MTD
- Potential for establishing >1 MTD
- Expand at predicted most efficacious MTD (may be more than one)
Phase II Design for 2NME Co-enhancement

• Goal: Evaluate the efficacy of 2NME Combo vs SOC and provide sufficient evidence that efficacy is due to combo

• Typically 4 arms (A+B, A, B and SOC)
  - Consider lead in with A+B vs SOC or adaptive design

• A and B arms at single agent MTD with cross-over to A+B on documented progression

• Phase III Go decision typically based on evaluation of PFS for A+B versus SOC

• Propose a general statistical design where the chance of falsely observing that A+B is highly active over A or B (observed PFS HR <0.7) is <20 %

• For most trials would require 40-50 patients treated with single agent A or B
Phase III Design for 2NME’s

- A Phase III label-enabling trial for a 2NME combination would be a randomized, two-arm trial comparing the efficacy and safety of the 2NME combo vs. SOC
- Primary endpoint as per indication and line of therapy
- Sample size and statistical plan typical for randomized Phase III
- Pre-specified rules for individual NME dose-reduction for toxicity
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September 14, 2009 • Washington, DC
Rationale for Modifying Current Regulatory Policies

James A. Zwiebel, M.D.
Chief, Investigational Drug Branch
Cancer Therapy Evaluation Program
DCTD, NCI
“But even most targeted therapies have limited impact. One reason is that most tumors are fueled by numerous, often redundant, genetic anomalies. That means that drugs with different targets need to be used in combination. But combinations increase both the costs and side effects of therapy. And it is difficult to test two experimental drugs in combination because the regulatory system is geared to assessing a single drug at a time.”

Andrew Pollack, New York Times
September 1, 2009
Sec. 300.50 Fixed-combination prescription drugs for humans.

The Food and Drug Administration's policy in administering the new-drug, antibiotic, and other regulatory provisions of the Federal Food, Drug, and Cosmetic Act regarding fixed combination dosage form prescription drugs for humans is as follows:

(a) Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug.

Special cases of this general rule are where a component is added:

(1) To enhance the safety or effectiveness of the principal active component; and

(2) To minimize the potential for abuse of the principal active component.
Design and Prioritization of Targeted Agent Combinations

Which targets?

• Maximize target inhibition
  – Antibody + small molecule tyrosine kinase inhibitor (TKI) to same target

• Maximize pathway inhibition
  – EGFR + Mek inhibitor

• Target multiple mechanisms/pathways
  – EGFR inhibitor + anti-angiogenic (+ others)
  – Overcome resistance / compensatory mechanism
**Selected Clinical trials for combination of novel/ target agents  (*sponsored by NCI)**

<table>
<thead>
<tr>
<th>Targets</th>
<th>Clinical trials</th>
<th>Tumor types</th>
</tr>
</thead>
<tbody>
<tr>
<td>Block parallel pathways</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Her-2 + Her-1</td>
<td>Trastuzumab + gefitinib*</td>
<td>Breast</td>
</tr>
<tr>
<td>↑↑ inhibition of one target</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VEGF + VEGFR/raf</td>
<td>Bevacizumab + Sorafenib*</td>
<td>RCC</td>
</tr>
<tr>
<td>EGFR + EGFR TKI*</td>
<td>C225 + Erlotinib*</td>
<td>Colon</td>
</tr>
<tr>
<td>Linear inhibition of pathway</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VEGF + mTOR</td>
<td>Bevacizumab + CCI-779*</td>
<td>RCC</td>
</tr>
<tr>
<td>Her-2 + mTOR*</td>
<td>Trastuzumab + Everolimus</td>
<td>Breast</td>
</tr>
<tr>
<td>EGFR + mTOR</td>
<td>Erlotinib + CCI-779*</td>
<td>NSCLC, Glioma</td>
</tr>
<tr>
<td>Her-2 + CDK*</td>
<td>Trastuzumab + flavopiridol*</td>
<td>Breast</td>
</tr>
<tr>
<td>Block multiple tumor process</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDAC + VEGF*</td>
<td>SAHA + Bevacizumab*</td>
<td>RCC</td>
</tr>
<tr>
<td>Vaccine + modulator</td>
<td>Vaccine + anti-CTLA4 Ab*</td>
<td>Melanoma, Prostate</td>
</tr>
<tr>
<td>Other</td>
<td>Bevacizumab + sunitinib</td>
<td>RCC</td>
</tr>
</tbody>
</table>

[www.clinicaltrials.gov](http://www.clinicaltrials.gov)
Combination Strategies

Tumor cell proliferation and survival

Migration Invasion

Angiogenesis

Growth Factors

Receptor Tyrosine Kinase

Ra

Raf

MEK

PI3K

Akt

mTOR

Growth Factors

Receptor Tyrosine Kinase

Ras

Raf-1

MEK

PI3K

Akt

mTOR

RTK Inhibitor

Erlotinib

Lapatinib

Ab to Receptor

Trastuzumab

Cetuximab

FTI

Tipifarnib

Raf Inhibitor

Sorafenib

MEK Inhibitor

AZD6244

PD032590

Anti-VEGF

Bevacizumab

VEGF-Trap

Anti-KDR

IMC101

KDR inhibitor

Sorafenib,

PTK787*,

Sunitinib,

AZD2171,

Pazopanib

mTOR Inhibitor

CCI-779

RAD001*

PKC

SRC

Apoptosis

BCL

XIAP

Cell cycle

CDKs

Protein Turnover

Hsp90

17AAG, 17DMAG

Proteosome

Bortezomib

Chromatin Remodeling

HDAC

SAHA

DNA

Methyltransferase

5-Aza-cytadine

Multiple Potential Interactions: HDAC inhibitors, Proteosome inhibitors
Bevacizumab + Sorafenib

**Rationale**
- Maximize target inhibition by hitting the ligand and the receptor
- Compensatory increase in VEGF due to VEGFR2 inhibition can be neutralized by bevacizumab.

**Toxicity concerns:**
- Will VEGF target toxicities be potentiated?
  - HTN,
  - Proteinuria
  - Bleeding
  - Bowel perforation
  - Arterial thromboembolism
# Bevacizumab + Sorafenib

## Two Phase I trials

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Sorafenib</th>
<th>Bevacizumab</th>
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<tbody>
<tr>
<td>1</td>
<td>200 mg bid daily</td>
<td>5 mg/kg q2wk</td>
</tr>
<tr>
<td>2</td>
<td>200 mg bid</td>
<td>10 mg/kg q2wk</td>
</tr>
<tr>
<td>3</td>
<td>400 mg bid</td>
<td>5 mg/kg q2w</td>
</tr>
<tr>
<td>4</td>
<td>400 mg bid daily</td>
<td>10 mg/kg q2w</td>
</tr>
</tbody>
</table>

1 (a) 200 mg bid (days 1-5) 5 mg/kg q2wk
2 (a) 200 mg bid (day 1-5) 10 mg/kg q2wk
3 (a) 400 mg bid (day 1-5) 5 mg/kg q2w

### Toxicity

- DLT: Proteinuria, hypertension, *hand-foot syndrome*
- Non-DLT SAE: bowel perforation/fistula, pulmonary hemorrhage
- MTD: 1/2 of the single agent doses; shorter duration

*From NCI intramural program, Vanderbilt U01*
<table>
<thead>
<tr>
<th>Combination</th>
<th>Full dose Tolerable?</th>
<th>DLTs</th>
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<tbody>
<tr>
<td>Bevacizumab + sorafenib</td>
<td>NO</td>
<td>HTN, Proteinuria, HFS</td>
</tr>
<tr>
<td>CCI-779 + Sorafenib</td>
<td>NO</td>
<td>HFS, Plts ↓, mucositis</td>
</tr>
<tr>
<td>CCI-779 + Erlotinib</td>
<td>NO</td>
<td>Mucositis, Rash, ↑ LFT, diarrhea</td>
</tr>
<tr>
<td>CCI-779 + bevacizumab</td>
<td>YES</td>
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</tr>
<tr>
<td>Erlotinib + Bevacizumab</td>
<td>YES</td>
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<tr>
<td>Erlotinib + Sorafenib</td>
<td>YES</td>
<td></td>
</tr>
<tr>
<td>Cetuximab + Bevacizumab</td>
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### Preliminary efficacy data

#### Combinations with promising preliminary (phase II or Phase III data still pending)

<table>
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<th>Cancer Type</th>
<th>Single agent data (historical)</th>
<th>Combination</th>
<th>Reference</th>
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<tbody>
<tr>
<td><strong>CRC (phase II)</strong></td>
<td>Cetuximab* (RR 8-10%)</td>
<td>Bevacizumab* (RR 3%)</td>
<td>Cetuximab + Bevacizumab (RR: 23%)</td>
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<tr>
<td><strong>Ovarian cancer (phase I)</strong></td>
<td>Sorafenib (RR: &lt;5%)</td>
<td>Bevacizumab* (RR: 18%)</td>
<td>Bevacizumab+ Sorafenib (RR: 4/14 (29%))</td>
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<td><strong>RCC (phase I)</strong></td>
<td>Sorafenib* (RR: 2%)</td>
<td>Bevacizumab* (RR: 10%)</td>
<td>Bevacizumab + Sorafenib (RR: 14/34 (41%))</td>
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<tr>
<td><strong>RCC (phase I)</strong></td>
<td>Temsirolimus* (RR: 7%)</td>
<td>Bevacizumab* (RR: 10%)</td>
<td>Bevacizumab+ CCI-779 (RR: high (n=12))</td>
</tr>
</tbody>
</table>

* Individual agents with proven activity in the setting
• The biological complexity of tumors requires a multi-targeted approach:
  – Strategies directed at single targets within tumor cells may fail, or, at best, may result in limited patient benefit
• CTEP has provided a mechanism for combining targeted agents from different sponsors
• Both empiric and rationale combinations have been safely assessed
• Potential supra-additive activity has been observed with some rationale combinations
However:

• Many sponsors are reluctant to sign a CRADA with CTEP unless NME has obtained proof-of-concept, or is approved, due to risks of assigning toxicity

• This results in significant delays in the development of promising investigational combinations

• *What is needed is a regulatory environment that facilitates the development and approval of new agent combinations*
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September 14, 2009 • Washington, DC
Panel 4: Combining Investigational Agents in Drug Development

Janet Woodcock
Standard Cancer Drug Development

• Investigational agent studied as single agent in first-in-human trials to determine toxicity profile and maximum tolerated dose
• May then be studied further as single agent (for example in advanced disease) or in combination with approved therapies
• Generally not studied in combination with other investigational drugs
FDA’s “Combination Rule”: 21 CFR 300.50

- Refers to fixed combinations: drugs physically combined
- States that, for approval, contribution of each agent to the effect must be demonstrated
- Usually done with factorial design trials: A vs B vs A+B
- Approach usually applied to combination regimens although not the subject of the rule
Points germane to Combination Rule

• Does not specify factorial trial design
• Other data have been accepted—for example, fixed combinations of decongestant and an analgesic—pharmacologic reasoning
• Compelling mechanistic data (in vitro or animal model data) can contribute to a conclusion that each agent has an effect
• If proposal is not to develop a fixed combination, the regulation does not apply
Combination Regimens

• Common in many conditions: hypertension; infectious disease; ischemic heart disease; cancer

• Efficacy trial designs commonly A+B+C (SOC) vs A+B+C+ investigational agent. Design does not evaluate unique contribution of each SOC agent in the presence of investigational agent.

• However, FDA would not want to approve a new combination regimen with two new agents unless each contributed to the effect
Co-development of Two Investigational Drugs in a Combination Regimen

- Need driven by better molecular understanding of mechanism of action combined with new targeted agents
- Issue is not confined to oncology
- For example, FDA has received inquiries about this issue for multi-drug-resistant tuberculosis where the issue of emergence of drug resistance is also important
Combination Regimen of Two Investigational Drugs

• Powerful biological rationale the most important factor

• Also: demonstrated medical need, i.e., population that does not have current adequate therapy

• Significant role for biomarkers:
  – Identify population appropriate for therapy
  – Pharmacodynamic response measures (is the target being hit/inhibited etc)
Expectations for Combination of Two or More Investigational Agents

- Severe or life threatening diseases
- Strong biologic rationale
- Expectation of highly clinically significant treatment effect—well beyond the small advances often seen in current new therapies
- Toxicities clearly outweighed by benefits—otherwise, would need to look at contribution to benefit and risk of each agent alone
White Paper Proposals

• Preclinical assessment of toxicity profile
• Phase 1 single agent toxicity evaluation
• Early assessment of response to single agent
• Later Phase 1 assessment of combination toxicity
• Either factorial Phase 2 design or combined, depending on biologic rationale/activity of each single agent
• Combination regimen Phase 3 efficacy trial vs SOC
• Comment: need to deal with the issues of appropriate biomarkers—they may also be co-developed
Steps for FDA

- Questions about combination regimens are being raised in many disease areas
- FDA needs to pursue a public process to establish policy in this area
- Combination rule is widely misinterpreted
- Plan: develop FDA guidance on topic
- Any party may submit proposals/draft guidances to FDA on policy topics