Development of Two Novel Therapeutics Targeting Multiple Pathways

C. Erlichman
Professor of Oncology
Mayo Clinic

Current State of Oncology Drug Development[1]

- 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

DiMasi J et al J. Clin Oncol:25:209;2007

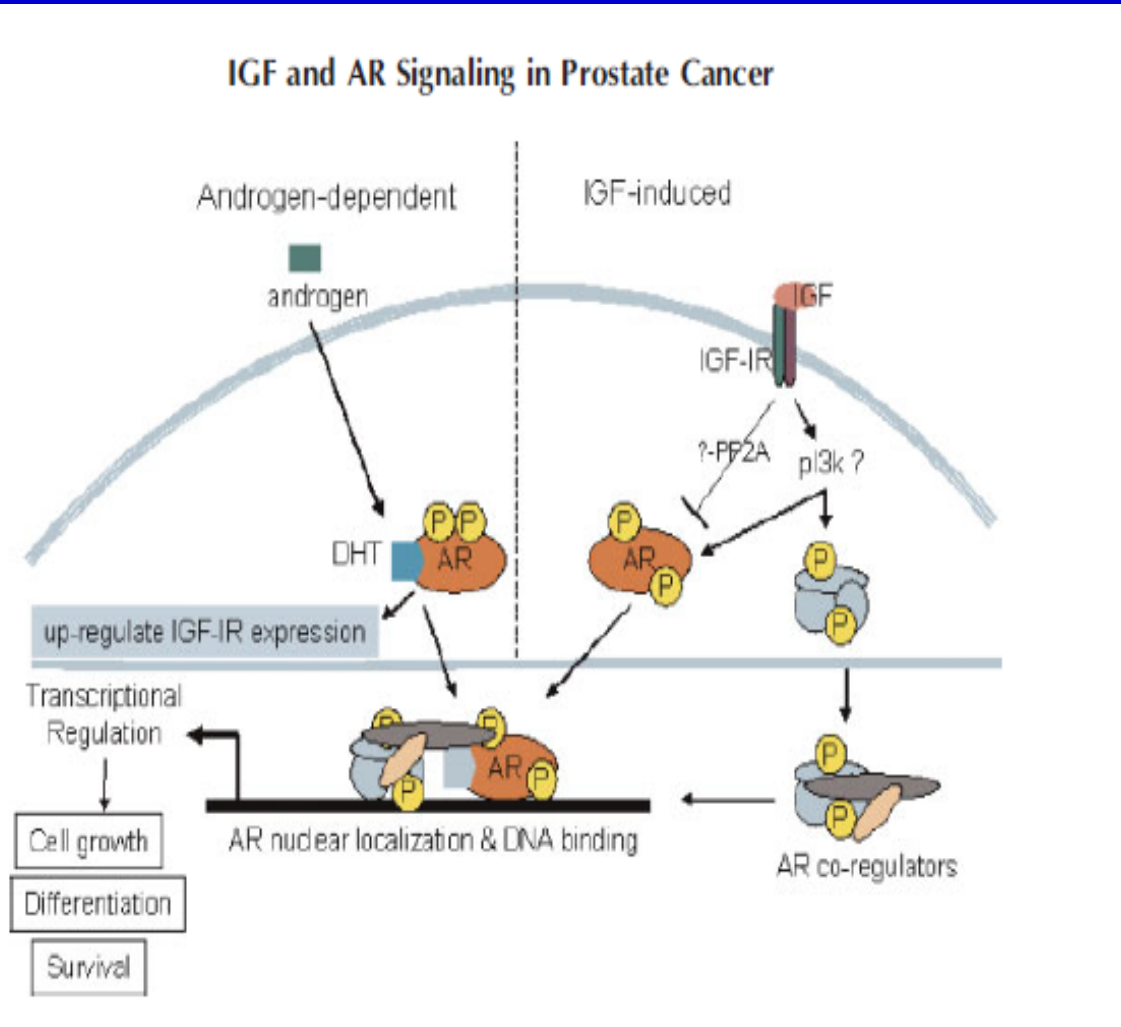
- Success rate of oncology drugs in phase

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

Crosstalk

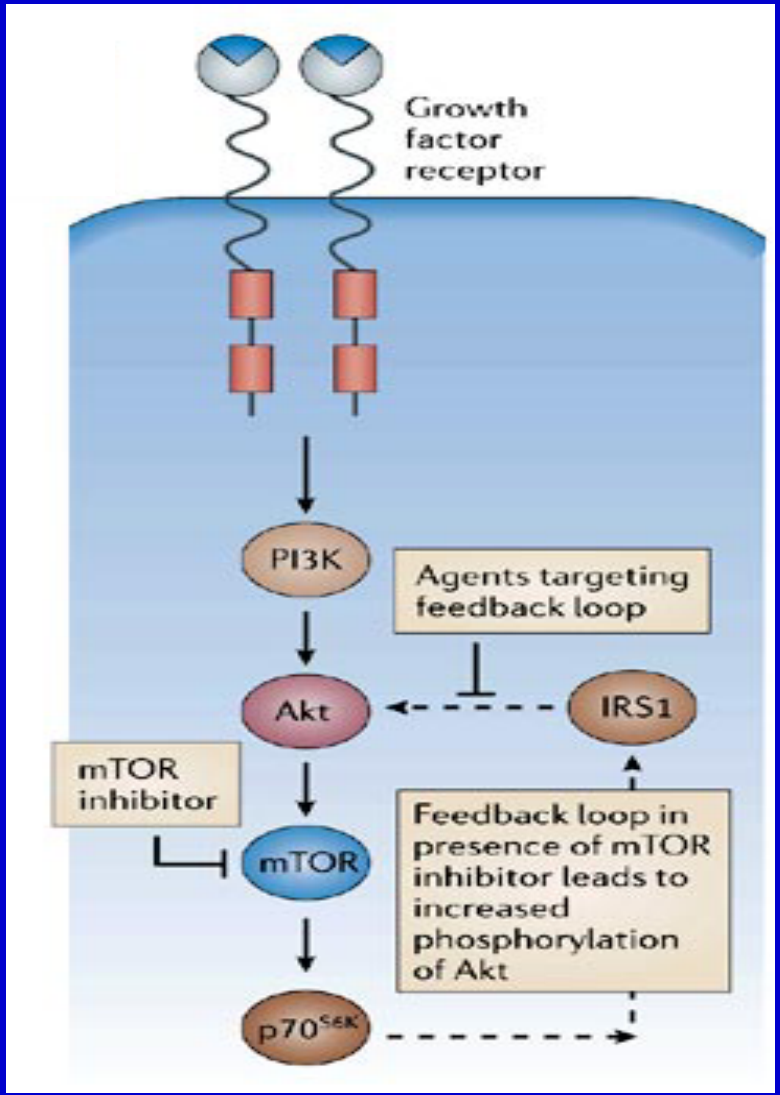
AR transcription may be enhanced through IGF1R activation of AR co-regulators



Wu JD et al J. Cell Biochem 99:392; 2006

Feedback

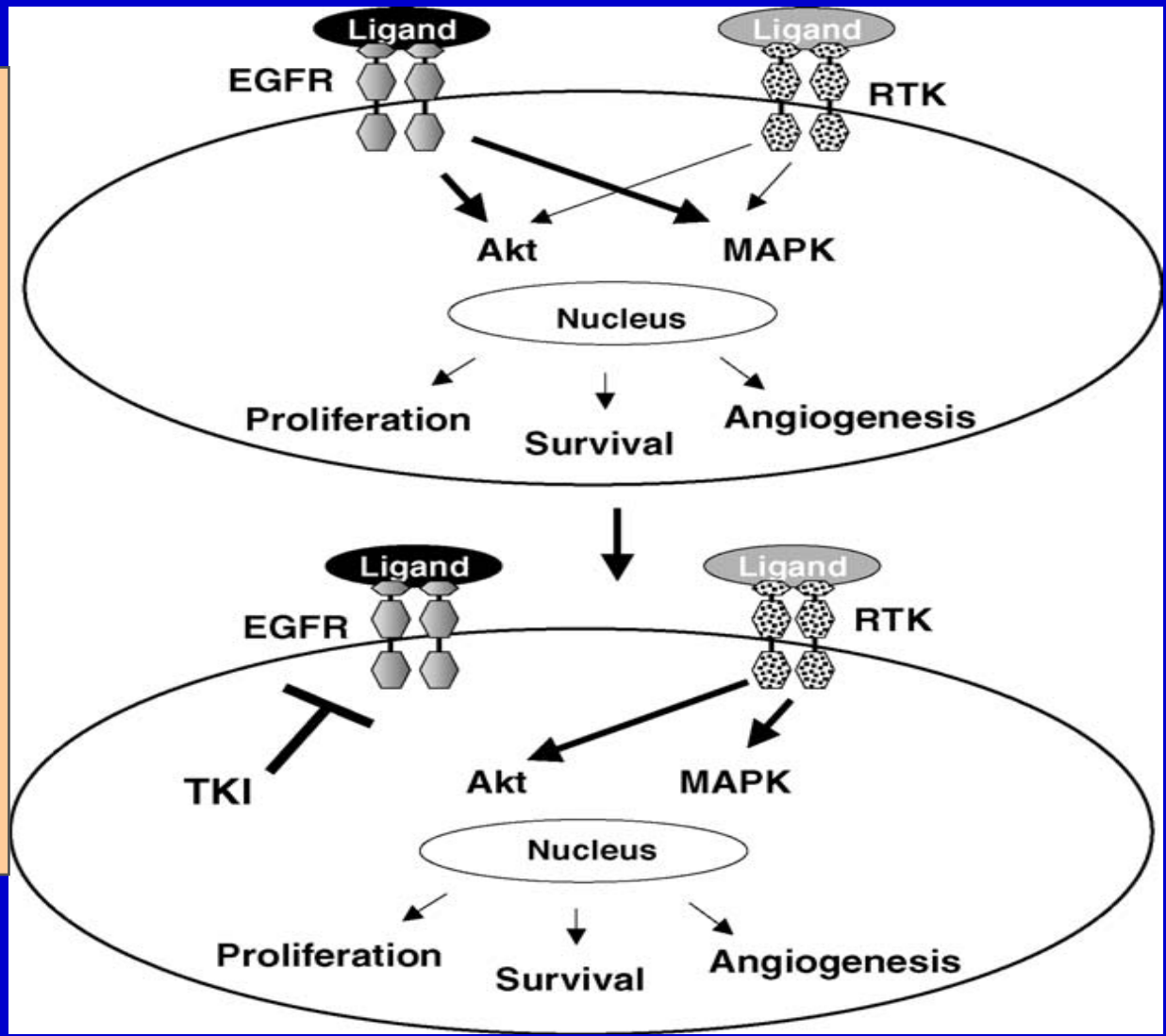
- Targeting mTOR can increase Akt activation
- Simultaneous targeting of PI3K-Akt may be synergistic



Dancey *et al. Nature Reviews Drug Discovery* **5**, 649–659 (August 2006) | doi:10.1038/nrd2089

REDUNDANCY

- 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

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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, tinnitis, vertigo)
- Peripheral neuropathy
- **Lung (pulmonary) Complications**

PATIENT'S OPINION IN THEIR PERSONALIZED CARE

"…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

WHY MODIFY CURRENT FDA PRACTICE?

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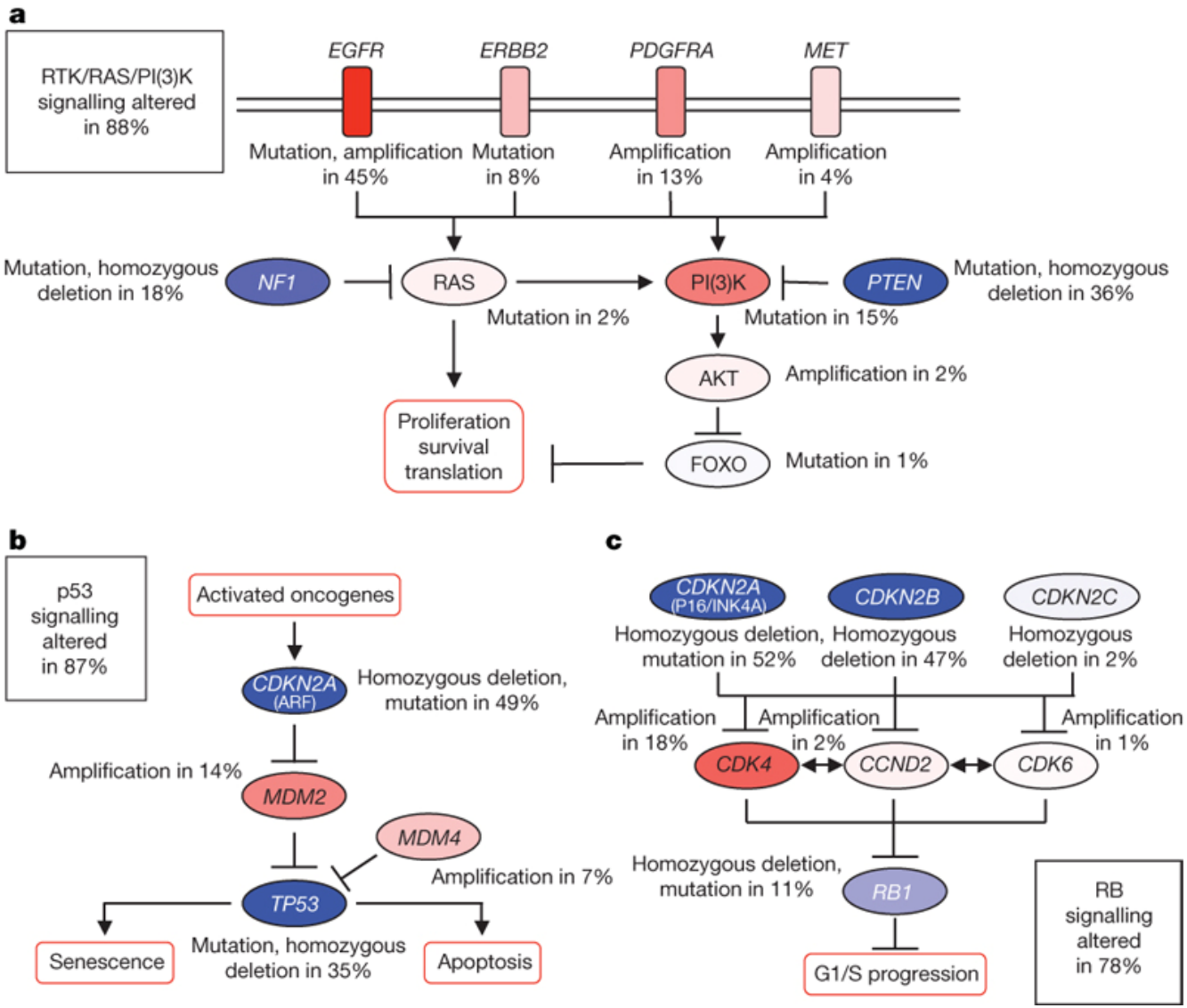
- 1960 Discovery of abnormal chromosome 22, the Philadelphia Chromosome in chronic myelogenous leukemia (CML) patients
- 1973 Lengthy chromosome 9 correlated with chromosome 22 deletion in CML
- 1982-87 Discovery of abl translocation and fusion with bcr
- 1996 Compound STI571 inhibits growth of BCR-ABL expressing cells
- 1999 Clinical trials for STI571
- 2001 FDA approval of Gleevec
- Total – 41years!

- Educational Network to Advance Cancer Clinical Trials (ENACCT) co-founded by LIVE**STRONG**
- LIVE**STRONG** Survivor*Care*
  - 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



Nature **455**, 1061-1068(23 October 2008)

THE FUTURE: TAILORING MULTIPLE NEW TREATMENTS

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- 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

SUMMARY: ACCESS AND OPTIONS

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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.

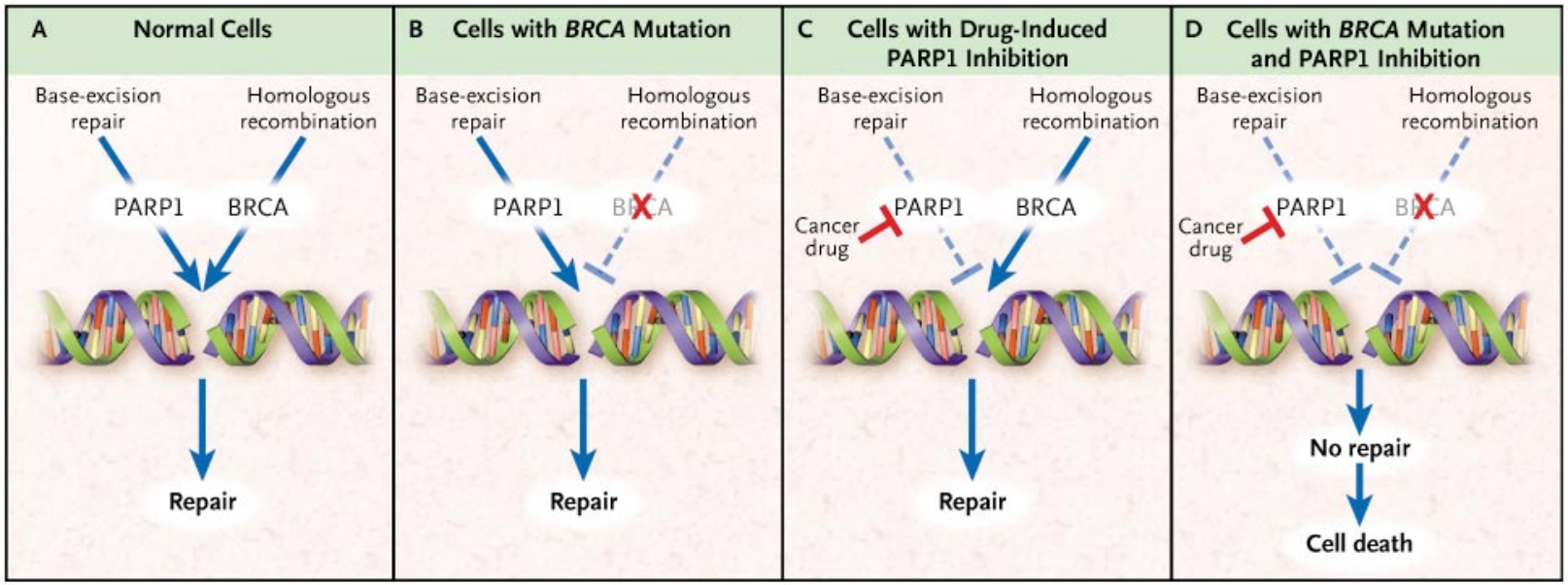
“Two defect hypothesis for cancer treatment to target the functional redundancy in living systems”

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)



Iglehart J and Silver D. N Engl J Med 2009;361:189-191

The NEW ENGLAND JOURNAL of MEDICINE

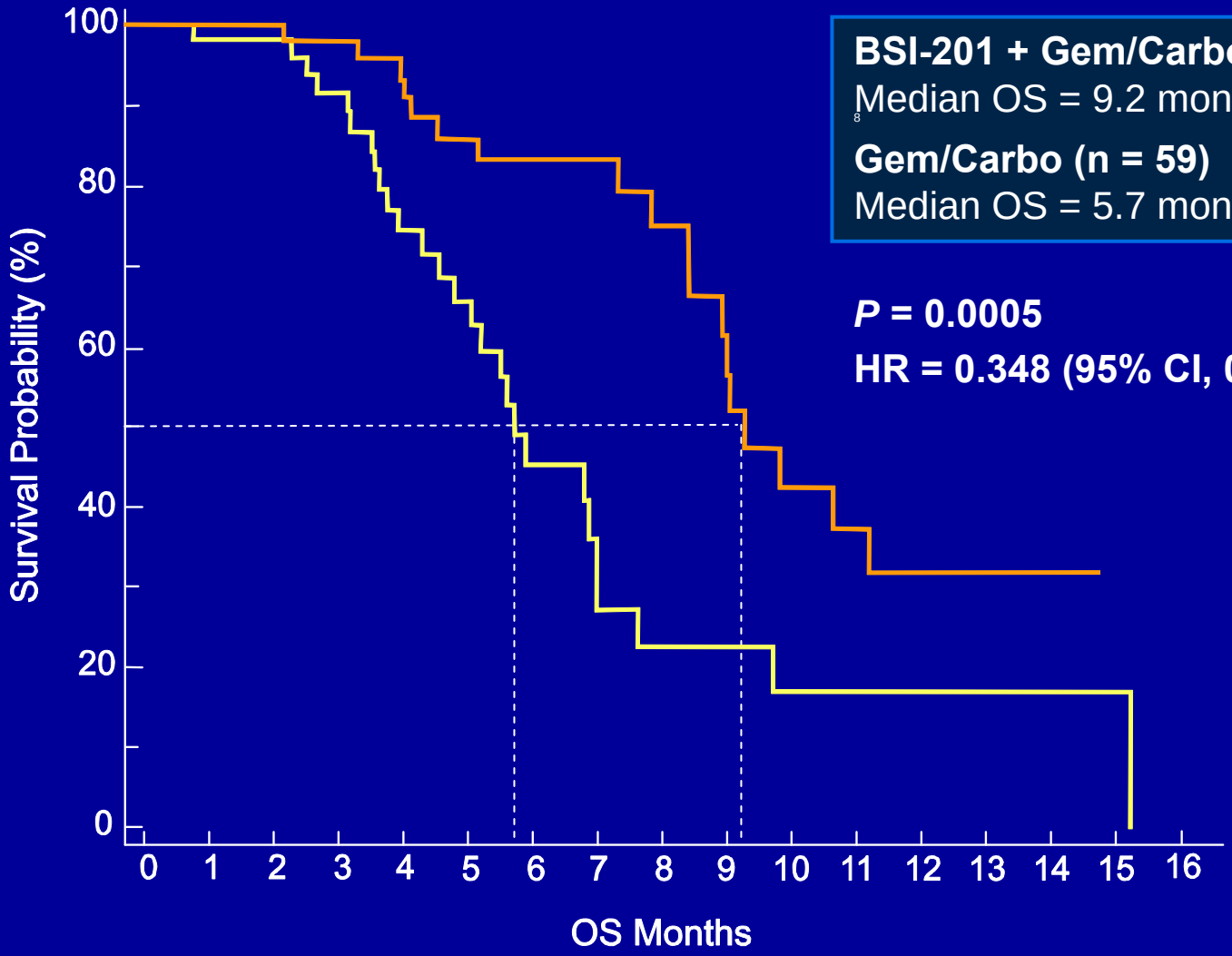
EXTENSION OF CONTEXT TO TNBC

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

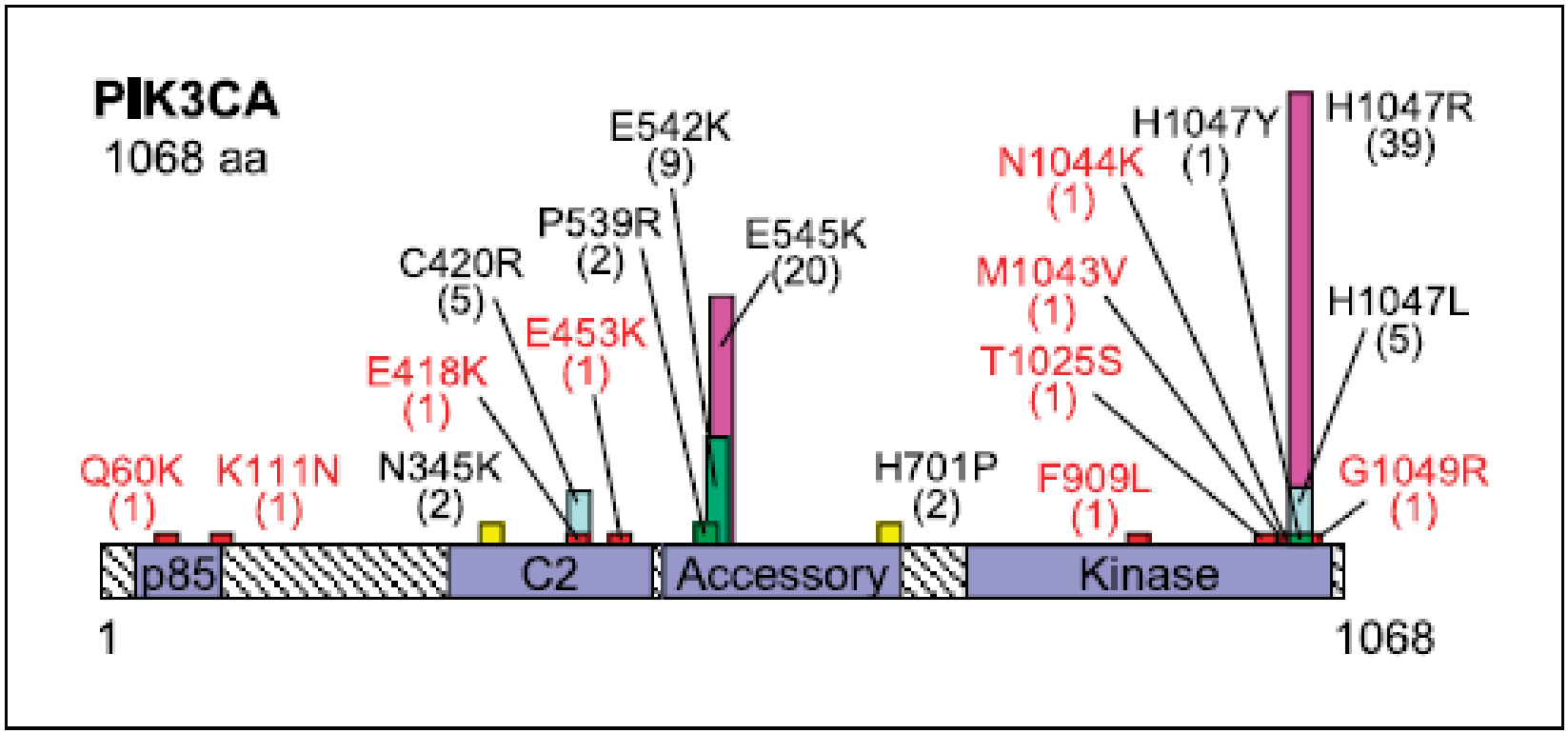
SYNTHETIC LETHAL CONTEXT 2

DEFECT IN CELL DEATH IN ER+ BREAST CANCER

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

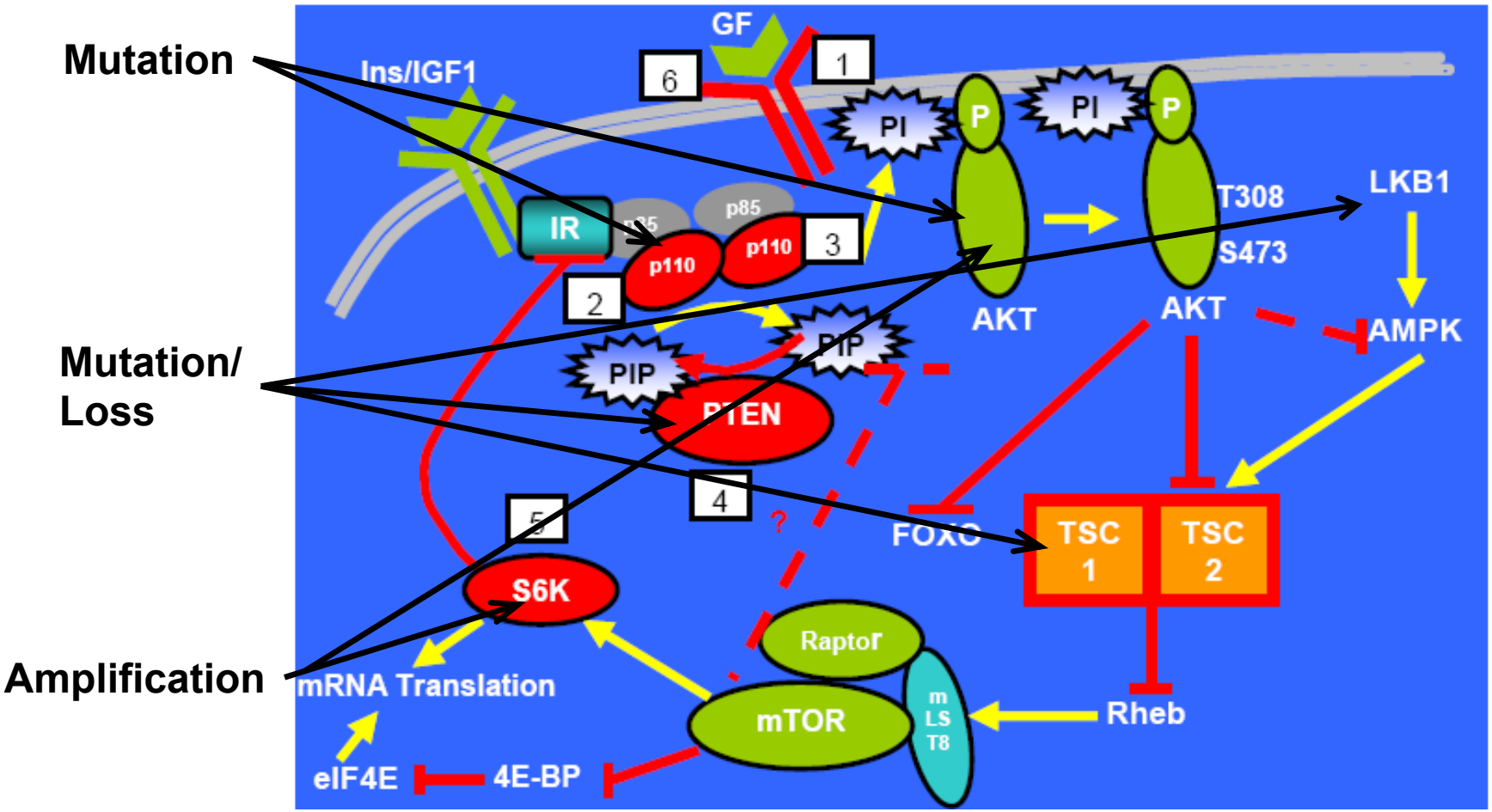
PI3KINASE MUTATIONS PREVENT ATROPHY OF ESTROGEN DEPENDENT ORGANS TO PRODUCE ESTROGEN DEPENDENT MALIGNANCIES

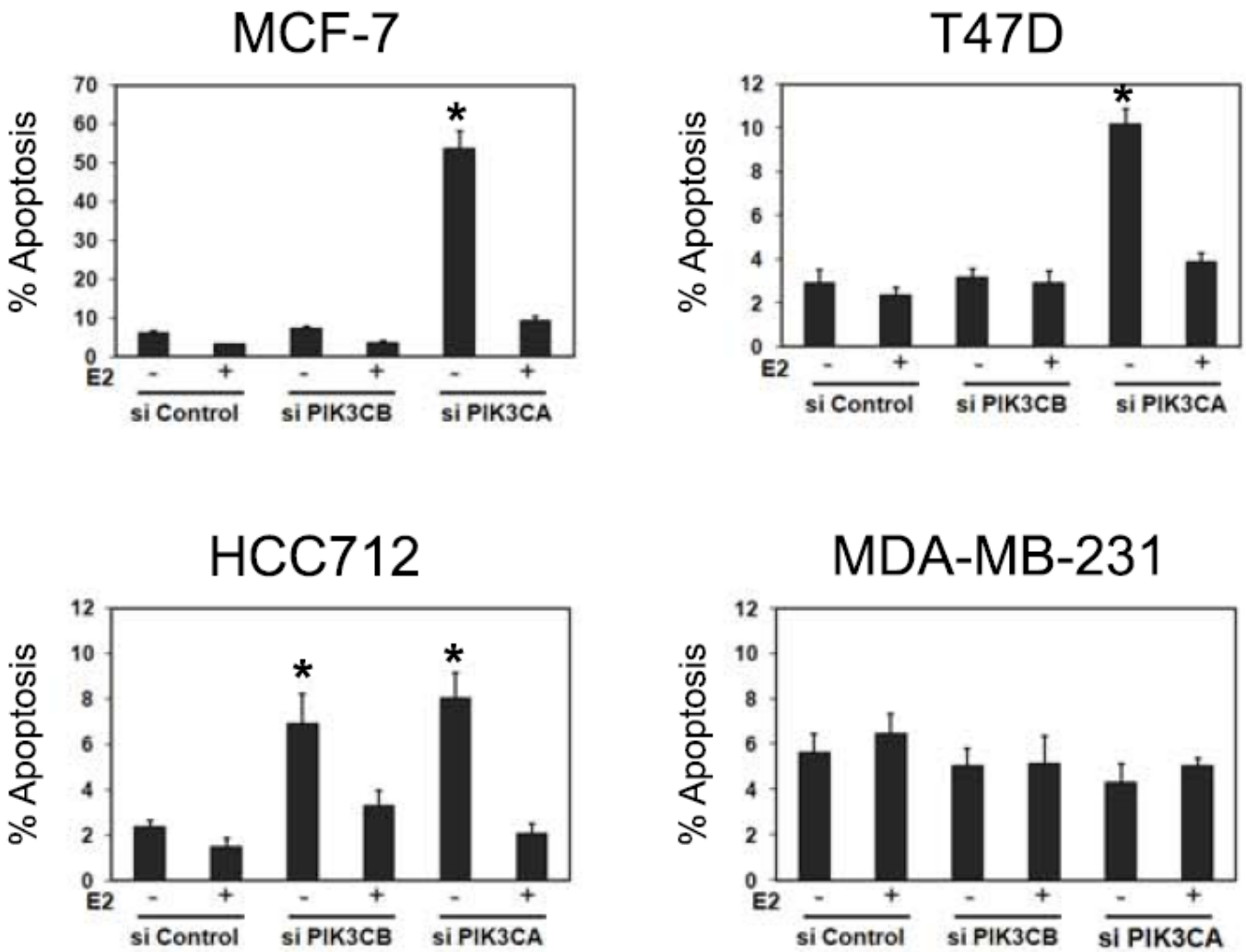
PIK3CA mutations are common in ER+ Breast cancer



About 30% of ER+ Breast Cancers have PIK3CA gain of function mutations

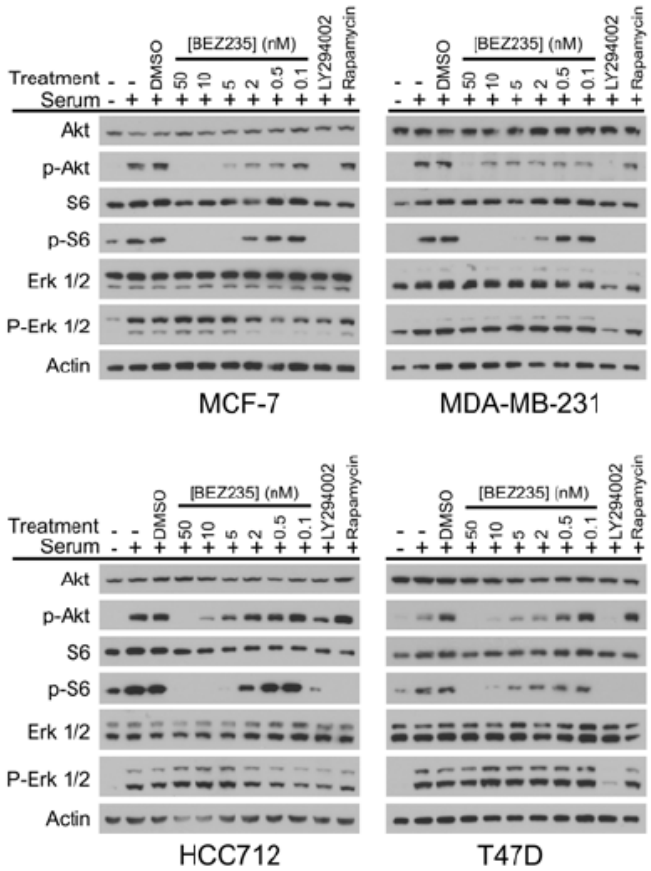
PI3K Pathway Signaling and Aberration in Breast Cancer



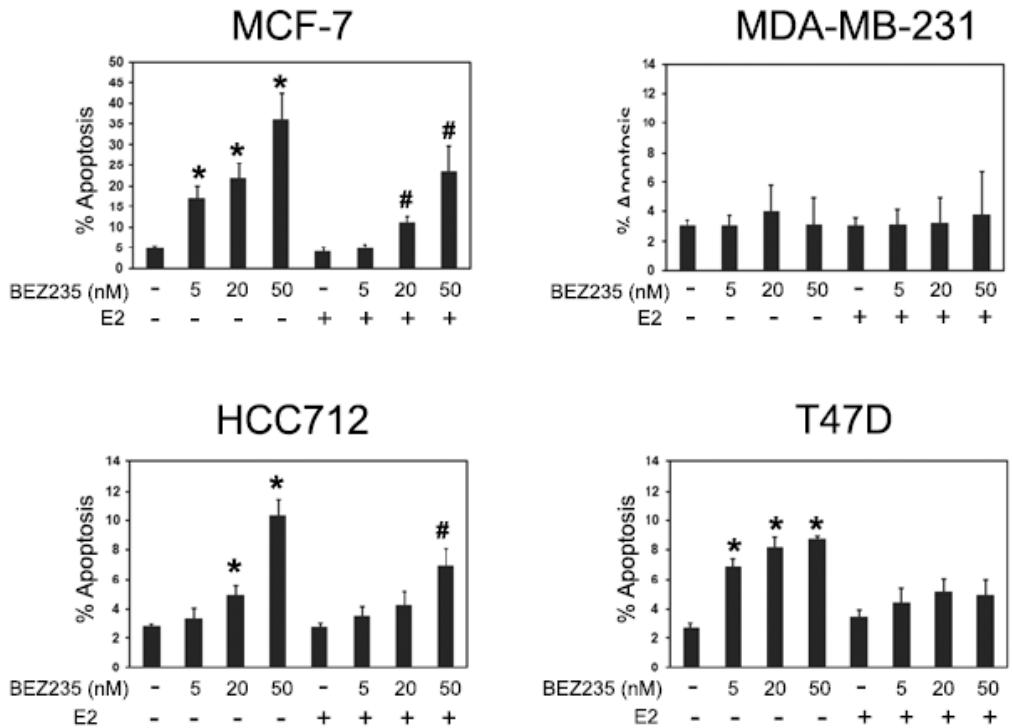


CROWDER, ELLIS ET AL CANCER RESEARCH 2009: 69, 3955

Cell Signaling



Cell Death



BEZ235 IC_{50}s:

p110α – 5 nM
p110β – 75 nM
mTOR – 20 nM

CROWDER, ELLIS ET AL CANCER RESEARCH 2009: 69, 3955

CONTEXT 2

DEFECT IN CELL DEATH

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

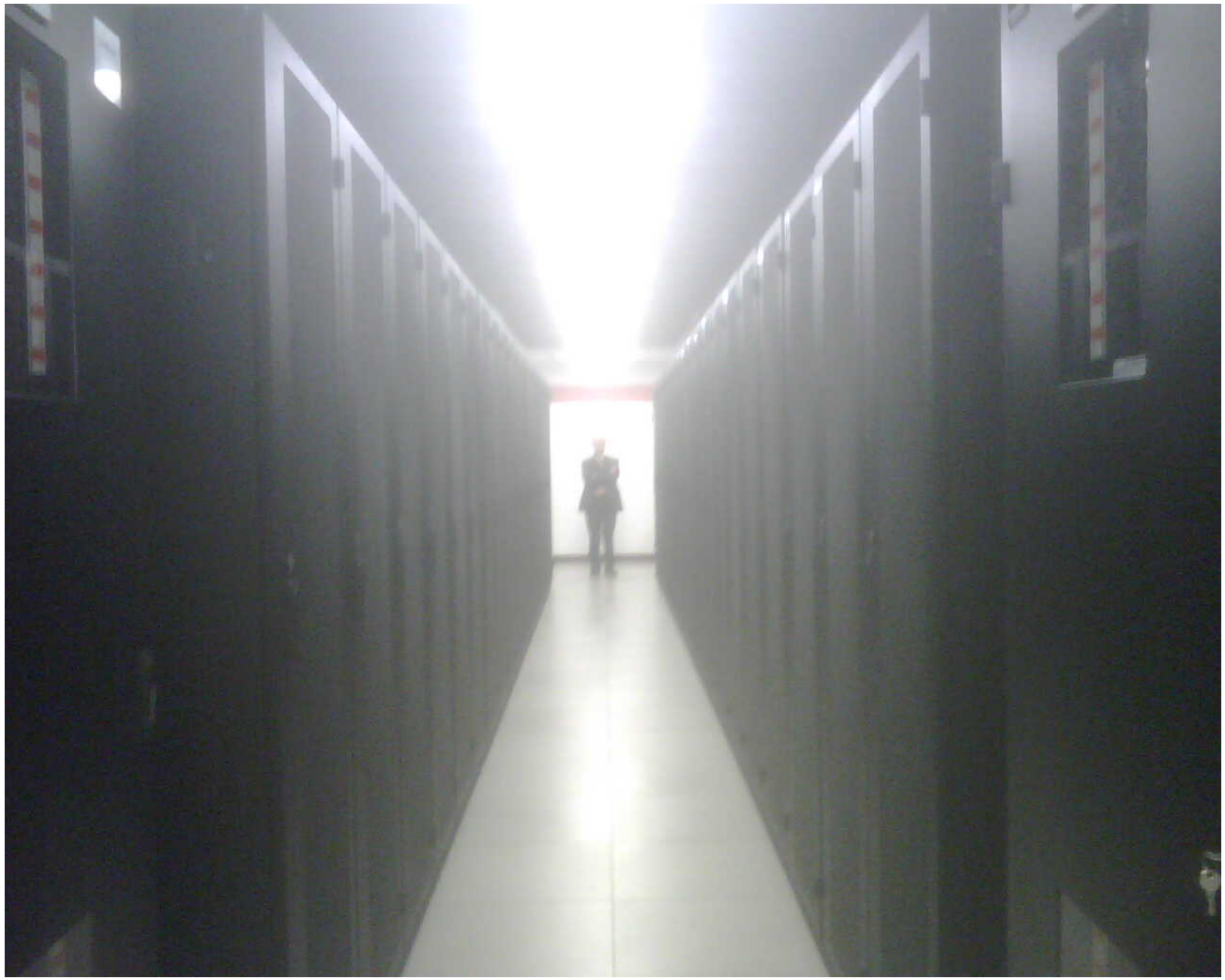
INHIBITION OF ESTROGEN PRODUCTION AND PI3KINASE INDUCES SYNTHETIC LETHALITY IN ESTROGEN-DEPEDENT ORGANS

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



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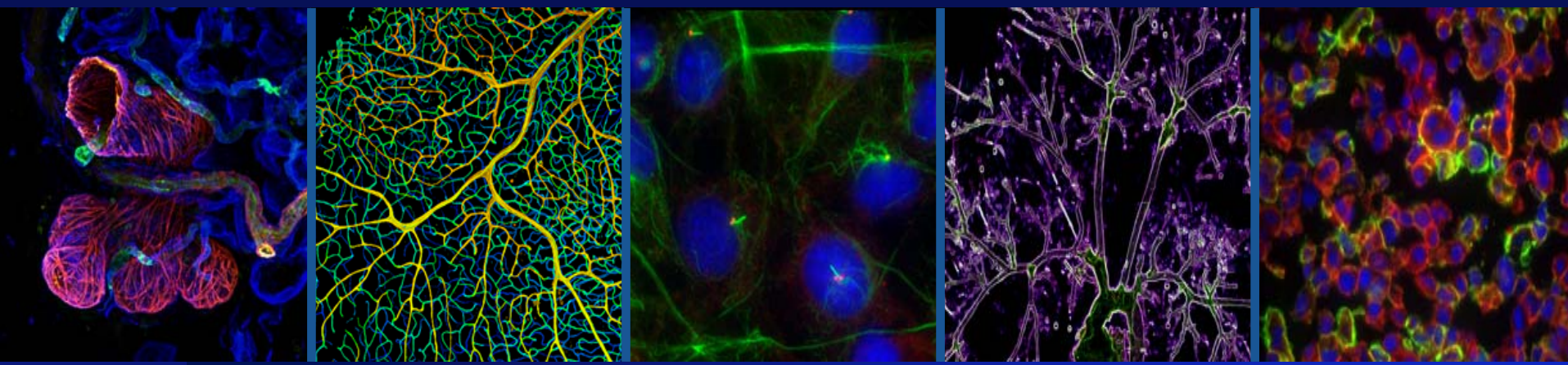
Clinical Evaluation of 2NME Combinations for Oncology Indications

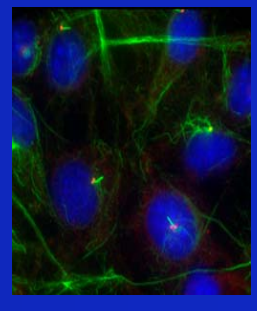
Stuart Lutzker, MD-PhD
Vice President
BioOncology Exploratory Clinical Development
Genentech Inc



Sept14th, 2009

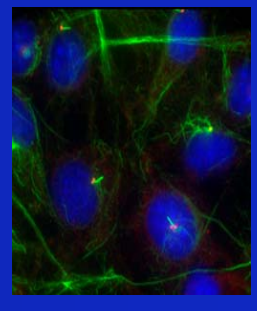
Genentech
A Member of the Roche Group

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 ?

Phase I NME

NME active with sufficient safety for pivotal study ?

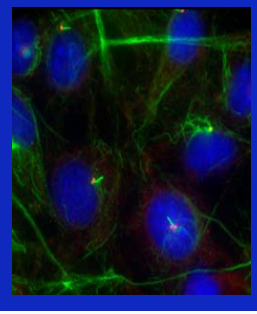
Randomized Phase II NME vs SOC

Statistically significant clinical benefit with adequate safety ?

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#*



Suitable PK and safety for the combo with adequate exposure ?

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

Combo active with adequate safety for pivotal study ?

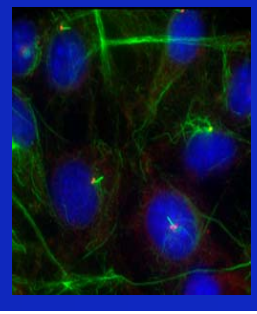
Randomized Phase II
NME A + NME B vs SOC

Statistically significant clinical benefit with adequate safety ?

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#*



Suitable PK, safety and TI ?

Phase I NME A

Phase I NME B

Safety with adequate exposure ?

Phase Ib
NME A + NME B

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

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

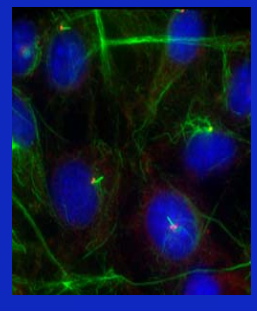
Statistically significant clinical benefit with adequate safety ?

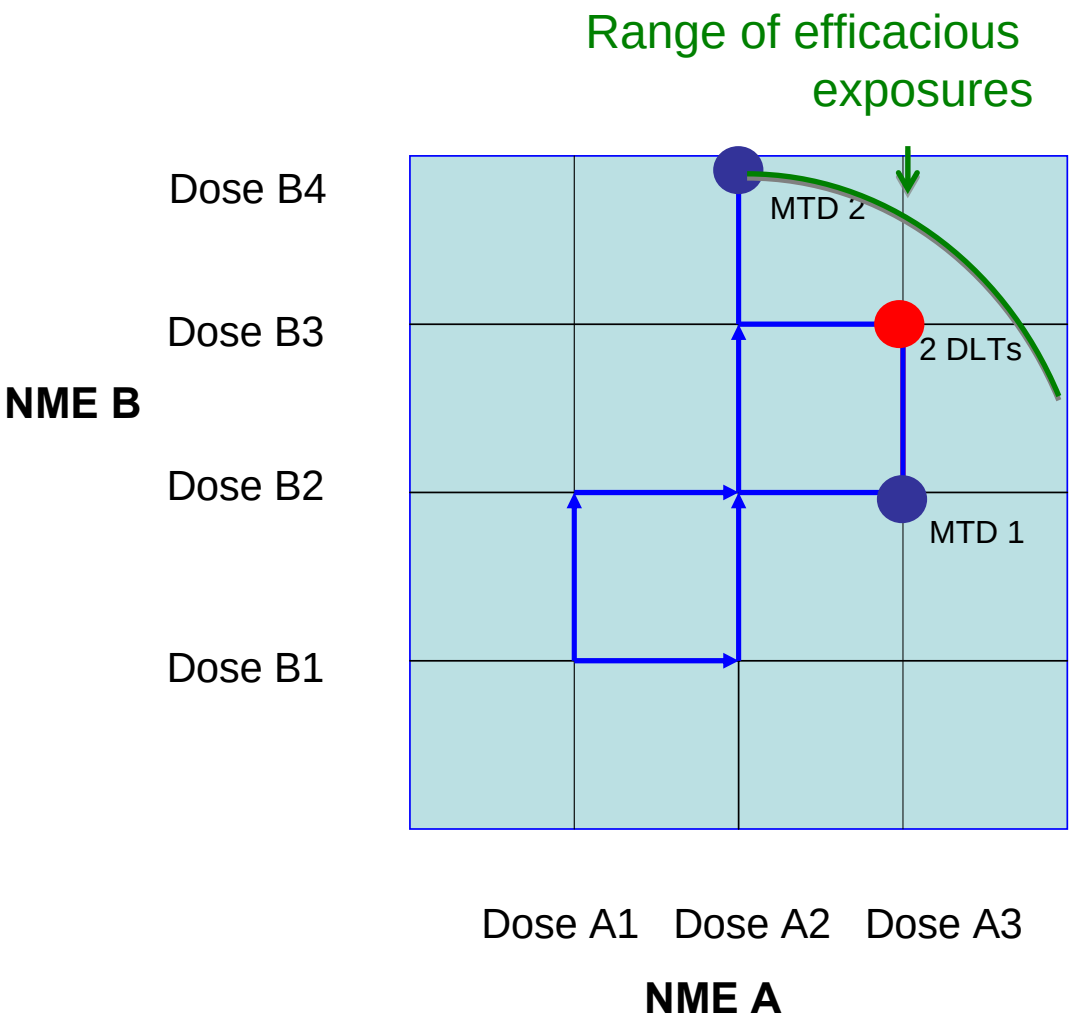
Randomized Phase III
NME A + NME B vs SOC

#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*

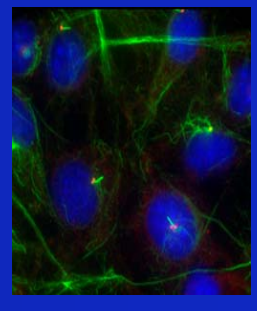
2NME Phase Ib Co-enhancement Dose Escalation Schema





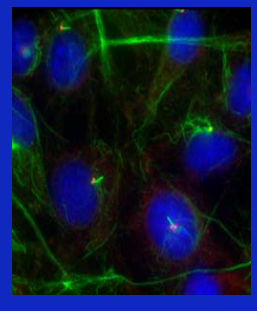
- **Dose escalate each NME in parallel to MTD (see example)**
- **Alternatively hold one NME constant while dose escalating other NME to MTD**
- **Potential for establishing >1 MTD**
- **Expand at predicted most efficacious MTD (may be more than one)**

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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National Cancer Institute

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

National Cancer Institute

21CFR300

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.

National Cancer Institute

Design and Prioritization of Targeted Agent Combinations

Which targets?

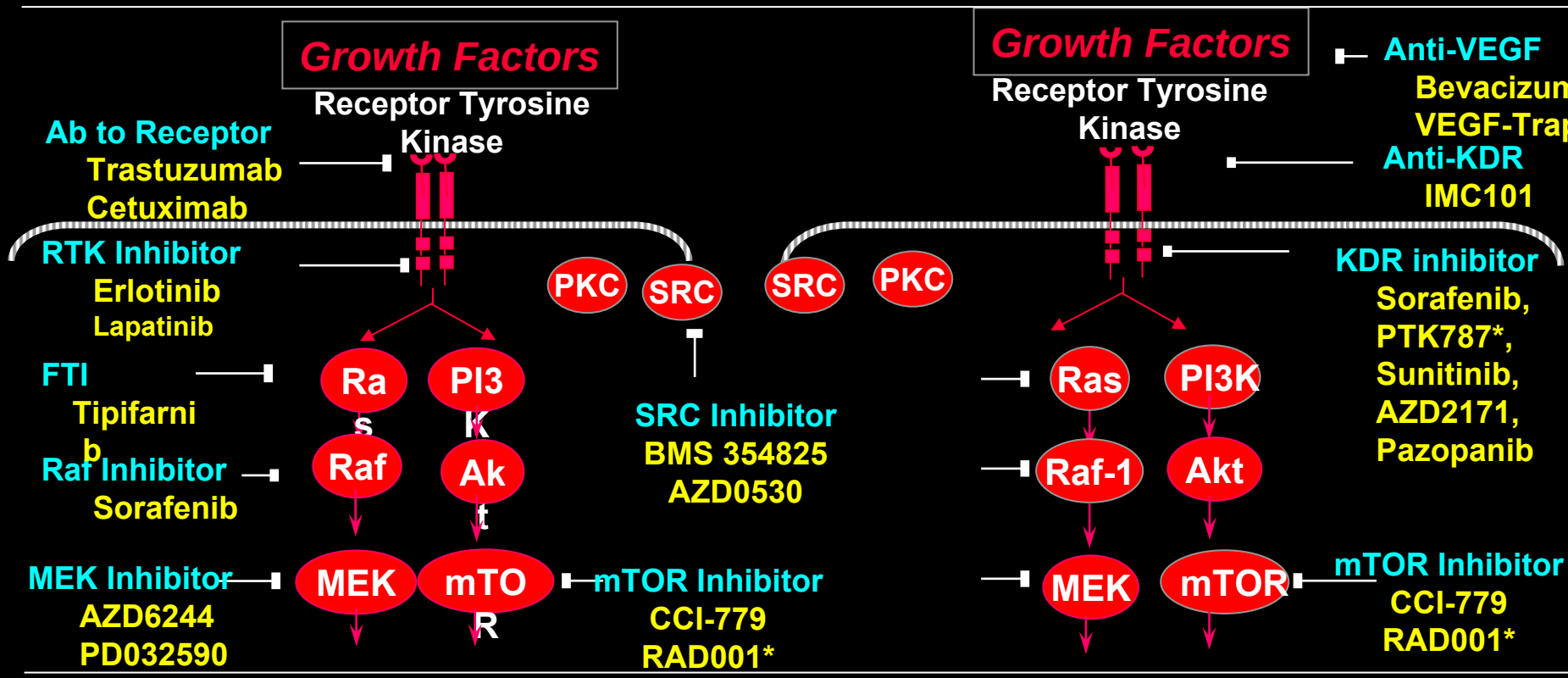
- Maximize *target* inhibition
  - Antibody + small molecule tyrosine kinase inhibitor (TKI) to same target
- Maximize *pathway* inhibition
  - EGFR + Mek inhibitor
- Target *multiple mechanisms/pathways*
  - EGFR inhibitor + anti-antiangiogenic (+ others)
  - Overcome resistance / compensatory mechanism

Selected Clinical trials for combination of novel/ target agents (*sponsored by NCI)

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

www.clinicaltrials.gov

Combination Strategies



Apoptosis

BCL

XIAP

Cell cycle

CDKs

Protein Turnover

Hsp90

17AAG, 17DMAG

Proteosome

Bortezomib

Chromatin Remodeling

HDAC

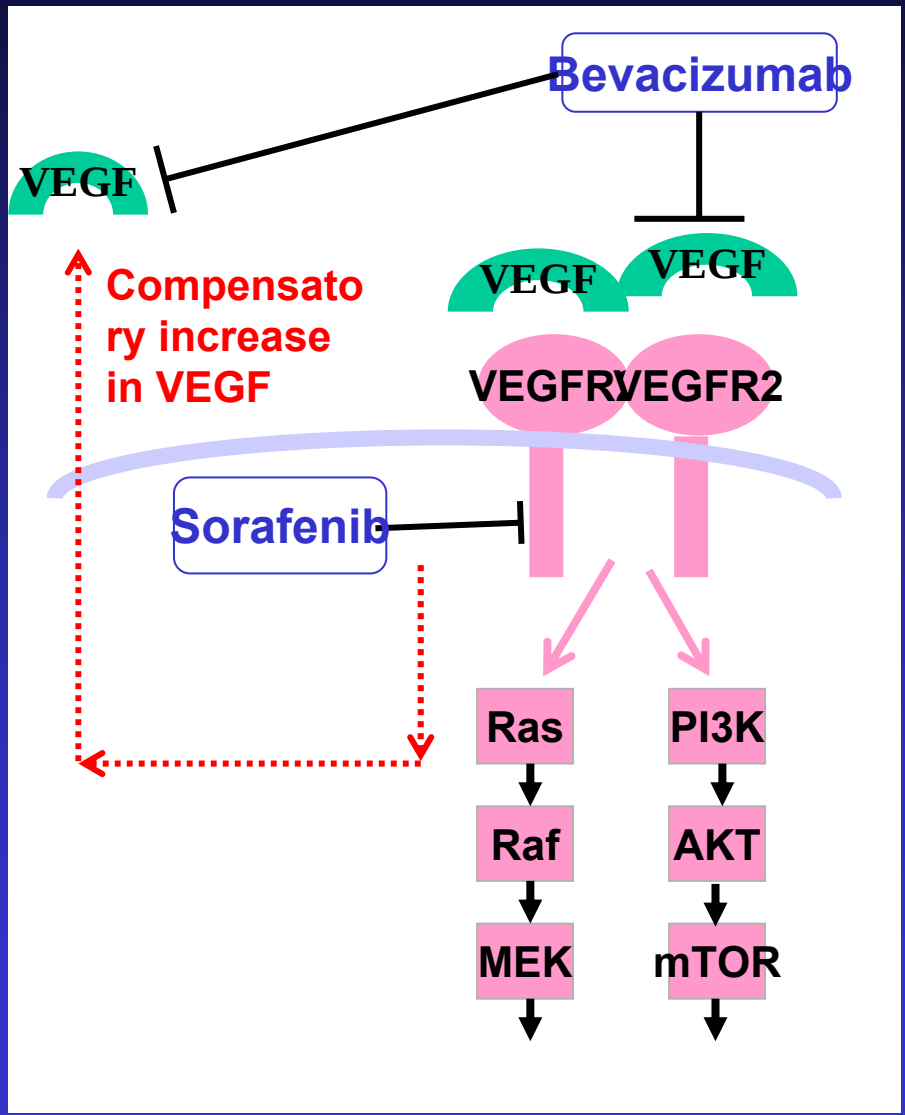
SAHA

DNA Methylatransferase

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

Dose Level	***Sorafenib***	***Bevacizumab***
1	200 mg bid daily	5 mg/kg q2wk
2	200 mg bid	10 mg/kg q2wk
3	400 mg bid	5 mg/kg q2w
4	400mg bid daily	10 mg/kg q2w
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

Not tolerable

Single agent full dose

MTD

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

Safety profile of other target agent combinations

	Full dose Tolerable?		DLTs
Bevacizumab + sorafenib	NO	• Sorafenib: 200 BID D1-5 • BV 5 mg/kg q2w	HTN, Proteinuria, HFS
CCI-779 + Sorafenib	NO	• Sorafenib: 200 BID • CCI: 25mg/m2	HFS, Plts ↓, mucositis
CCI-779 + Erlotinib	NO	• CCI: 15 mg/m2	Mucositis, Rash, ↑ LFT, diarrhea
CCI-779 + bevacizumab	YES		
Erlotinib + Bevacizumab	YES		
Erlotinib + Sorafenib	YES		
Cetuximab + Bevacizumab	YES		

Preliminary efficacy data

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

	Single agent data (historical)		Combination	
CRC *(phase II)*	*Cetuximab** •*RR 8-10%*	*Bevacizumab** •*RR 3%*	Cetuximab + Bevacizumab • **RR: 23%**	*Saltz, ASCO 2005*
Ovarian ca *(phase I)*	*Sorafenib* •*RR: <5%*	*Bevacizumab ** •*RR: 18 %*	**Bevacizumab+ Sorafenib** • **RR: 4/14 (29%)**	*Azad et al, ASCO 2006*
RCC *(phase I)*	*Sorafenib** •*RR: 2%*	*Bevacizumab** •*RR: 10%*	**Bevacizumab + Sorafenib** • **RR: 14/34 (41%)**	*Sosman et al, ASCO 2006*
RCC *(phase I)*	*Temsirolimus** •*RR: 7%*	*Bevacizumab** •*RR: 10%*	**Bevacizumab+ CCI-779** • **RR: high (n=12)**	*Merchan*

* Individual agents with proven activity in the setting

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Summary

- 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

National Cancer Institute

Summary – cont''d

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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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 a 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