The Good, The Bad, and Ugly

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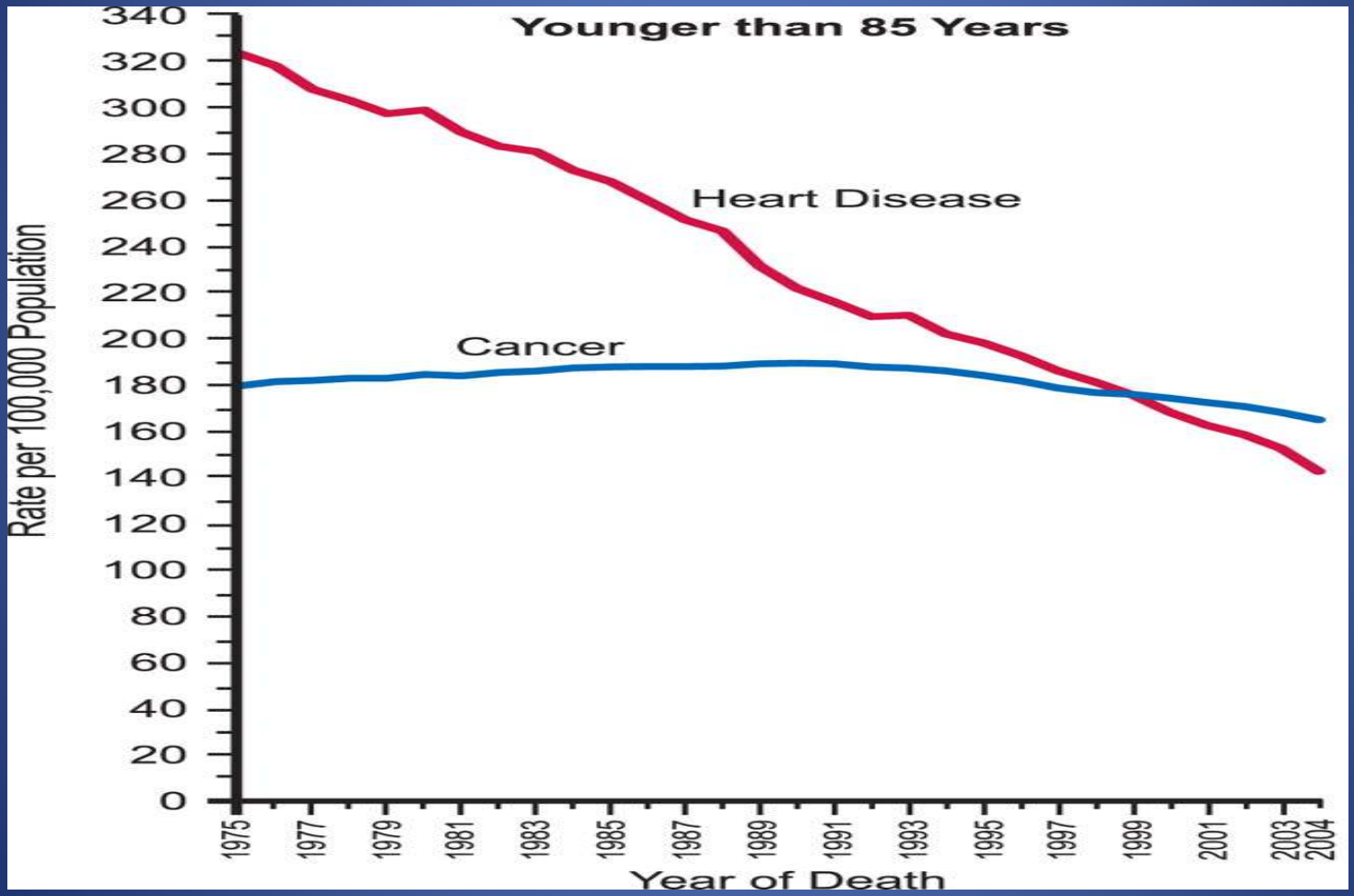
The Good, The Bad and The Ugly

Cancer now causes 23% of all US deaths & is leading cause of death in those aged <85 yrs

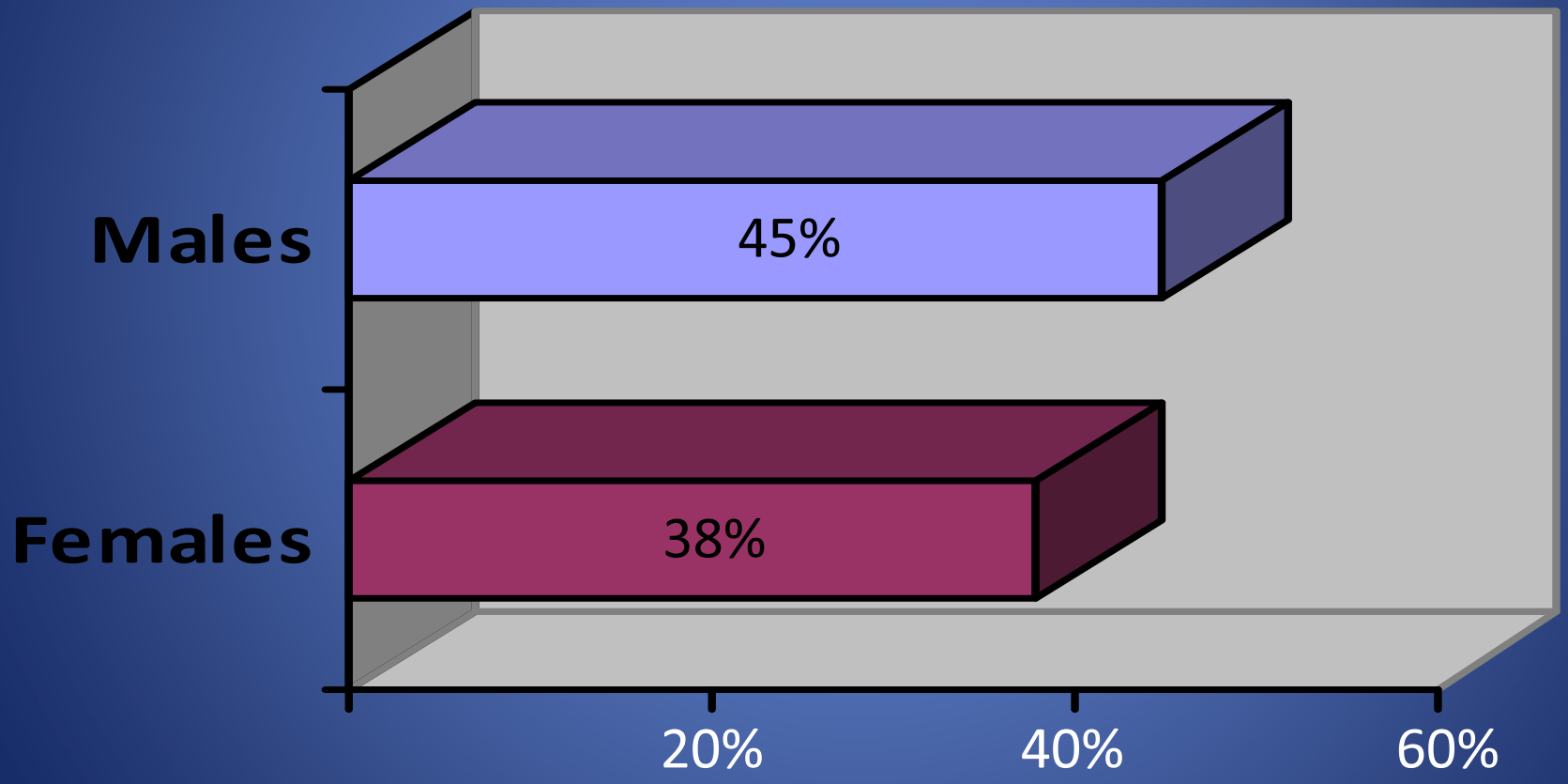


From Jemal, A. et al.
CA Cancer J Clin 2008;58:71-96.

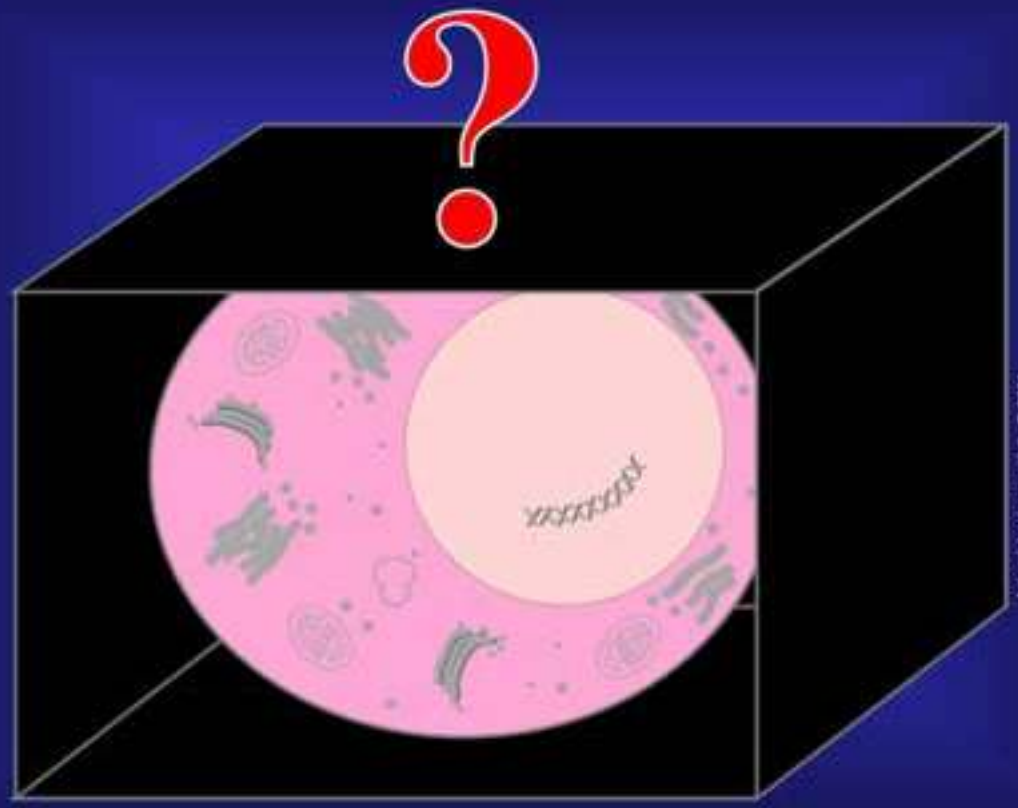
Every 57 seconds another American dies of cancer: 63 over the past hour

Life-time probability of developing cancer:

A problem coming soon to a family near you?

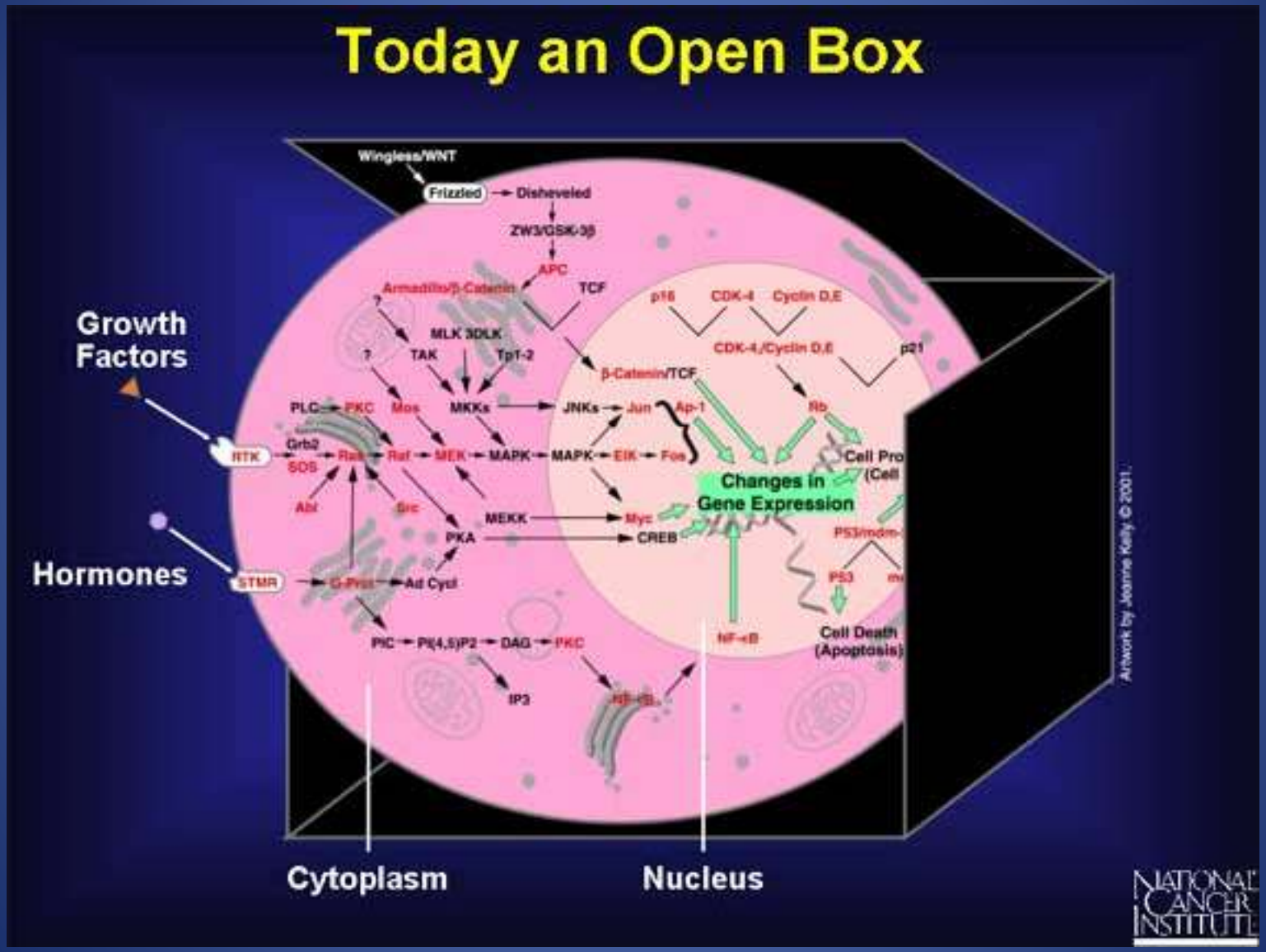


Once a Molecular Black Box



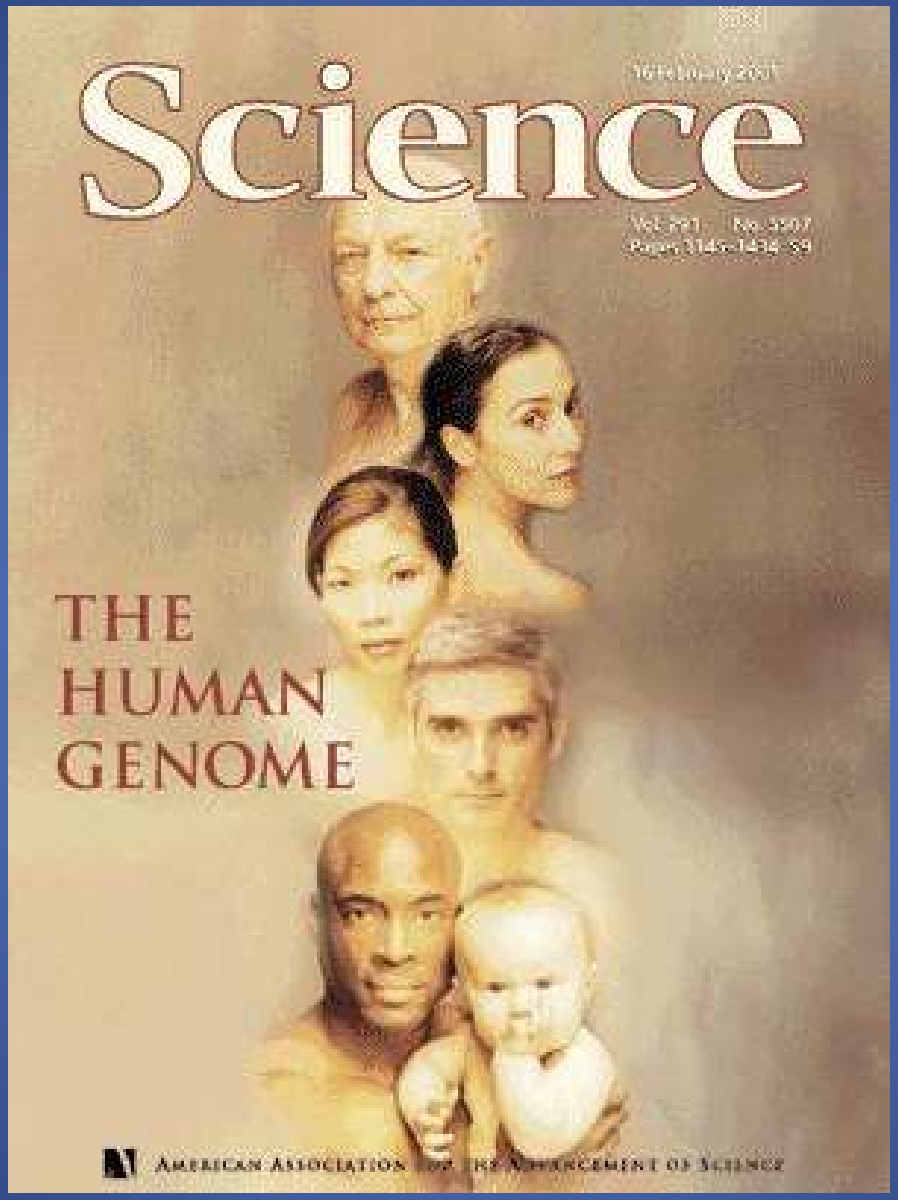
NATIONAL CANCER INSTITUTE

Today an Open Box



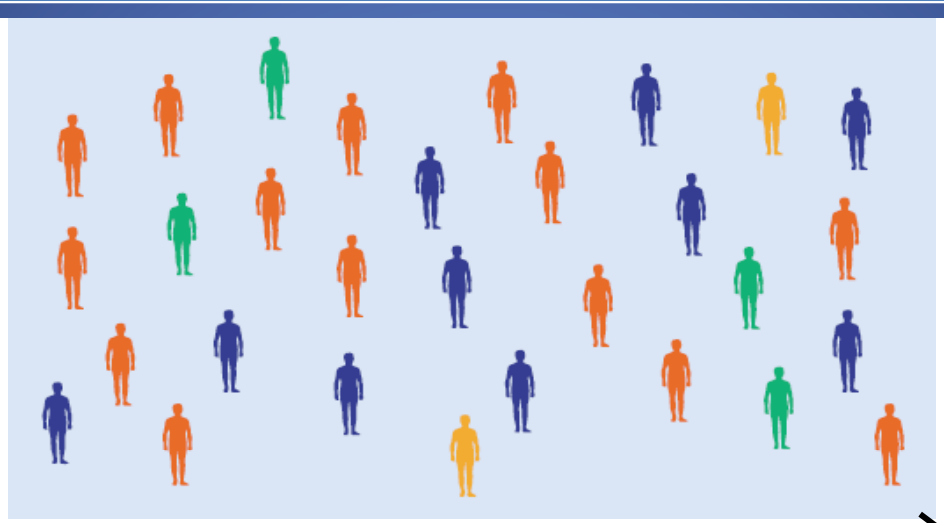
New Directions in Oncology

- Angiogenesis
- Apoptosis
- Signal Transduction
- Immunotherapy
- Other Targets
- Personal Therapy

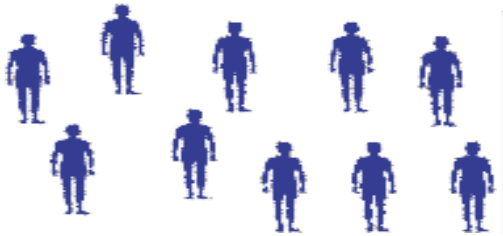

Science
THE HUMAN GENOME

PERSONALIZED CANCER MEDICINE

PATIENTS WITH SAME DIAGNOSIS ARE NOT ALL THE SAME

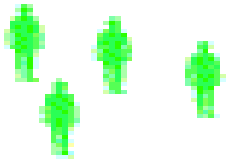


Predicted good response to drug or combination of drugs



Predicted poor or no response to drug or combination of drugs

CHANGE DRUGS



Increased likelihood of toxicity of drug or combination of drugs

CHANGE DRUGS

The Regulatory Traffic Jam

Factors Behind the Regulatory Traffic Jam

US Gov't Agencies:

FDA

NCI

OHRP

CLIA

HIPAA

IRS

MEDICARE

OFFICE INSPECTOR GENERAL

PATENT OFFICE

JAHCO

TORT LAWS

→ Massive Regulatory Traffic Jam →

Costs ↑↑

Delays ↑↑

Frustrations ↑↑

Efficiency ↓↓

New ideas tested ↓↓

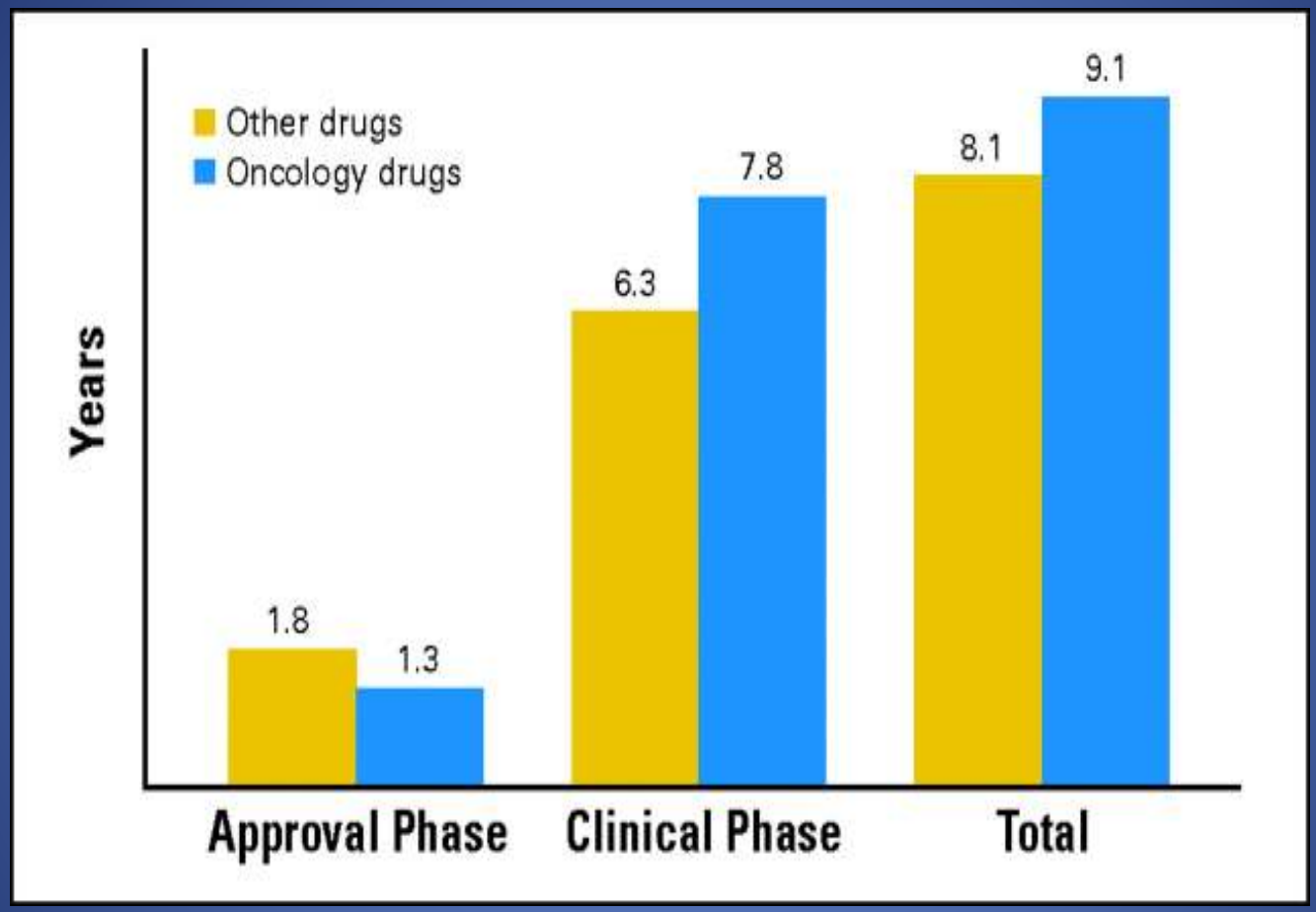
Investigator initiated trials ↓↓

US competitiveness ↓↓

Rate of Progress ↓↓

Lives lost

The ↑↑ costs mean you can't do trials without lots of funding → those with the money then drive the agenda!



Dimasi JA, Grabowski HG. JCO 2007

The New York Times

Grant System Leads Cancer Researchers to Play It Safe. NY Times, June 6th 2009

"These grants are not silly, but they are only likely to produce incremental progress," said Dr. Robert C. Young, chancellor at Fox Chase Cancer Center in Philadelphia and chairman of the Board of Scientific Advisors

Los Angeles Times

Medical clinical research slows for lack of patients. Shari Roan March 14, 2009

"Enrollment problems delay more than 70% of clinical trials from one to six months, according to a 2007 survey by CenterWatch, a Boston-based company that publishes information on clinical trials. In cancer care, less than 5% of patients enter clinical trials, even though more than 700 cancer therapies -- many that are highly promising -- clog the research pipeline."

The New York Times

Target Cancer

New Drugs Stir Debate on Rules of Clinical Trials. Amy Harmon, September 18th,2010

Mission

To translate laboratory discoveries and clinical observations into hypothesis-driven clinical trials leading to targeted, tailored and personalized cancer treatments

Dept of Investigational Cancer Therapeutics
Timeline

- July 04: Phase I Program initiated
- Sept 04: Phase I Clinic started
  (Clinical Center for Targeted Therapy)
- March 05: Phase I Inpatient Service started
- July 07: Dept of Investigational Cancer Therapeutics established

Investigational Cancer Therapeutics
Distinguishing Features

- Treatment is not disease-based but target-based.
  Diverse cancers treated.

- Treatment is based on early phase clinical trial.
  Correlative/translational aspects are critical.

- Treatment is not conventional. Virtually all patients are on trial.
  Specialized business center
  Regulatory infrastructure

What kinds of trials do we do?

- Studies with new first-in-human molecules
- Trials of new combinations of experimental or approved drugs
- Protocols using new routes of delivery of drugs

Pt H (42/F) (Castleman's disease): Rx = anti-IL-6 Ab [CNTO328]

Castleman's Disease is driven by IL-6

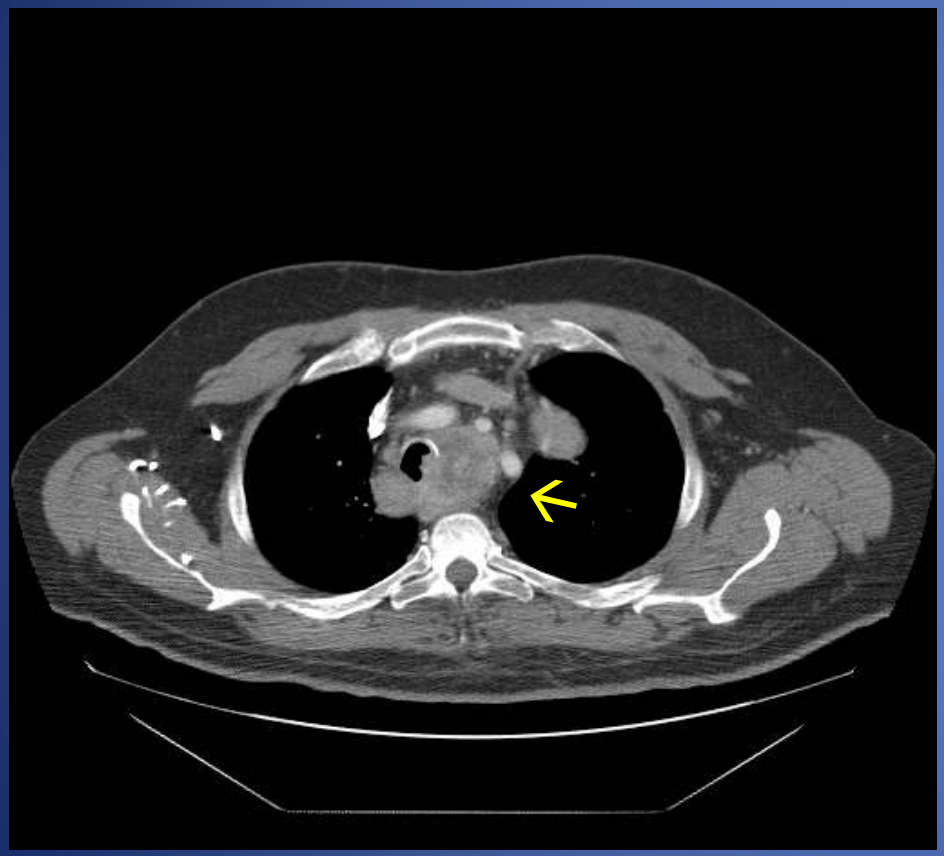
Pt H (Baseline)

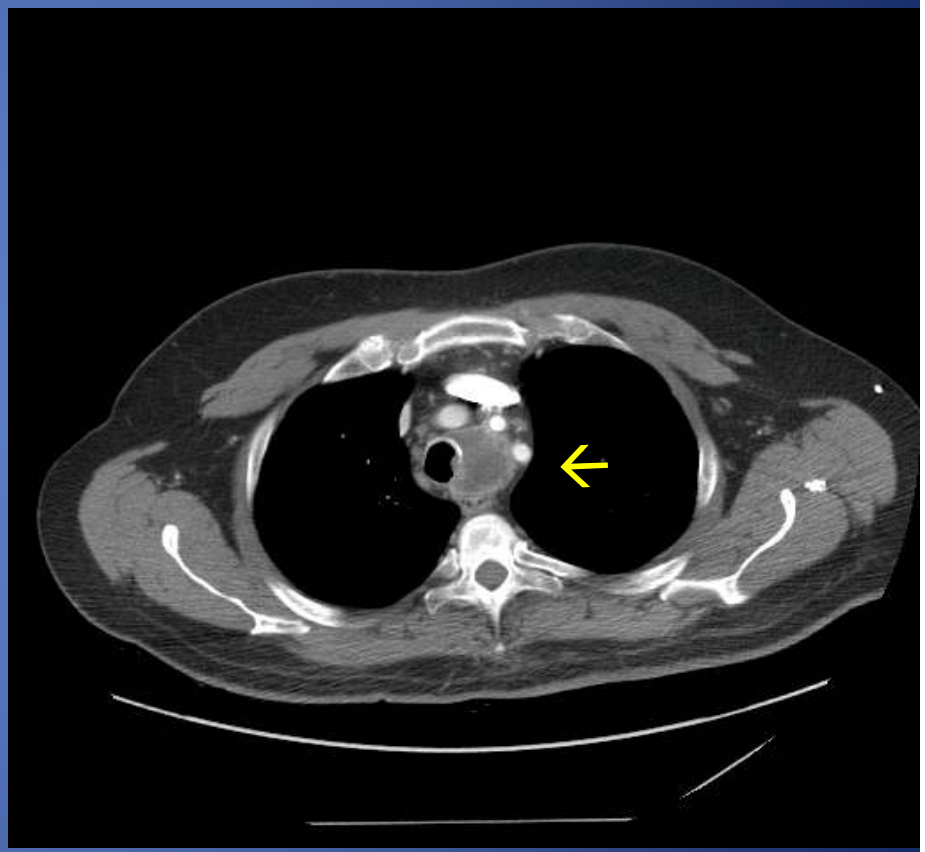
Pt H s/p 2 doses

Pt H s/p 6 doses

12/14 patients with Castleman's on study have responded

Pt X (55/M) (medullary thryoid cancer)
Treatment = RET kinase inhibitor XL184

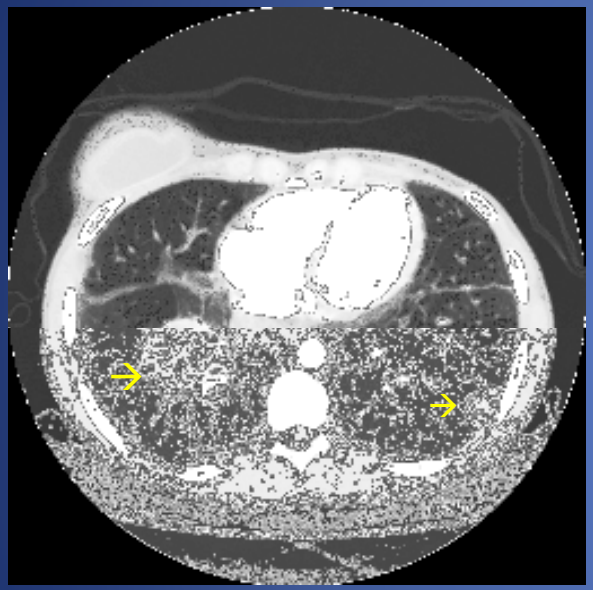




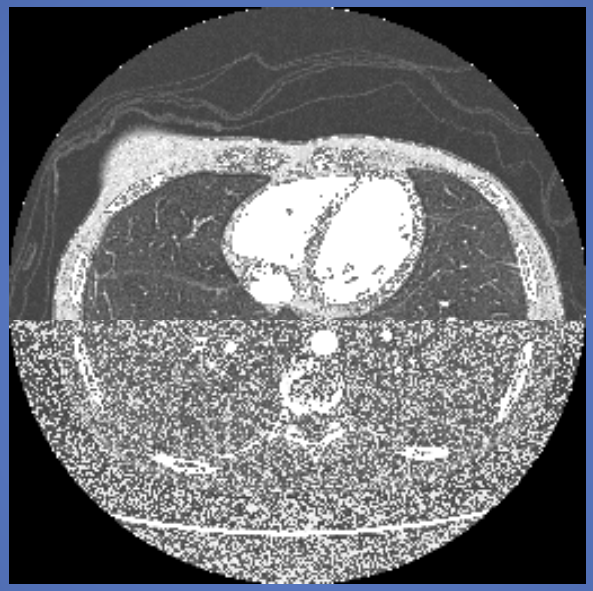
Pre-Treatment

Post-Treatment week #3

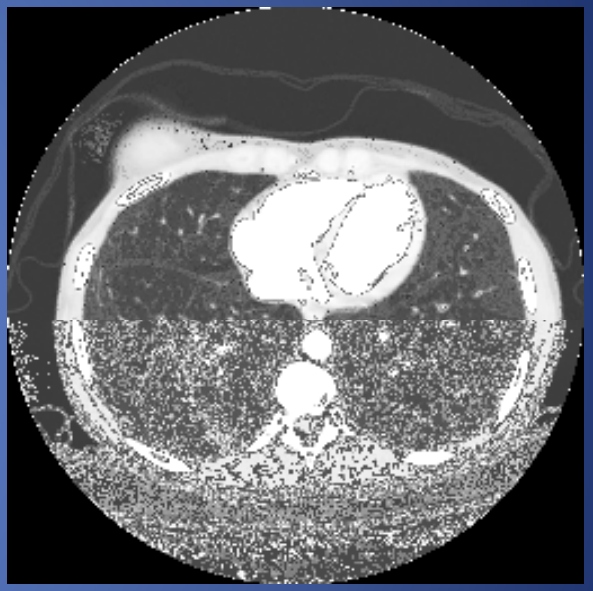
Pt M (28/F) (Ewing's sarcoma): Rx = IGFR Inhibitor



Dec. 8, '06



Jan. 25, '07



Mar. 1, '07

Histology-Independent Target-Based Trials

BRAF inhibitor: BRAF mutation+
(thyroid, melanoma, colon etc)

MEK inhibitor: Raf+ or Ras+ mutations

PI3K or mTOR inhibitor: PI3K+ mutations/PTEN loss

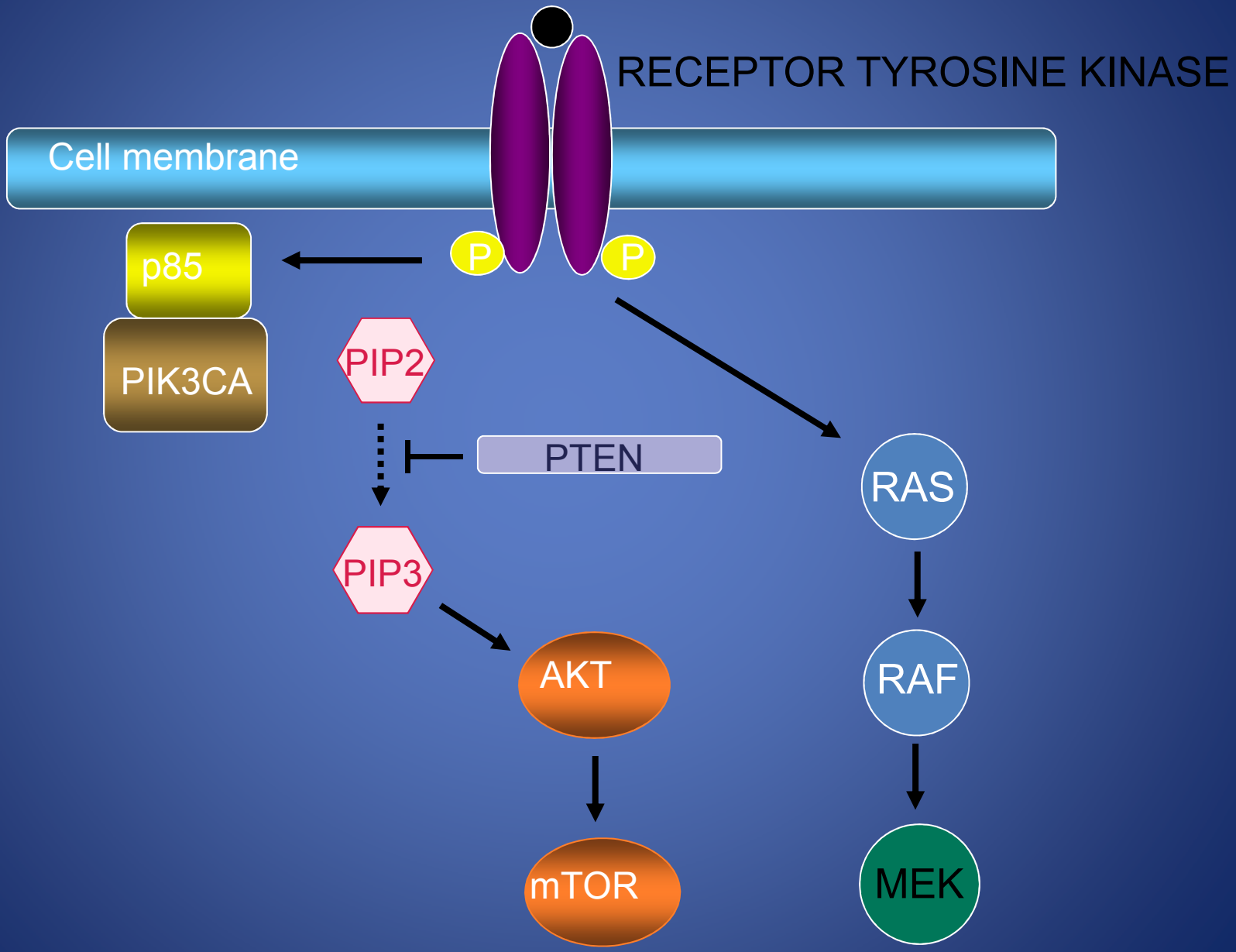
PI3K plus MEK inhibitor: PI3K+ mutation or PTEN loss &
Ras+ or Raf+

Personalized Targeted Cancer Therapy

PREDICT

Profile-**R**elated **E**vidence **D**etermining **I**ndividualized **C**ancer **T**herapy

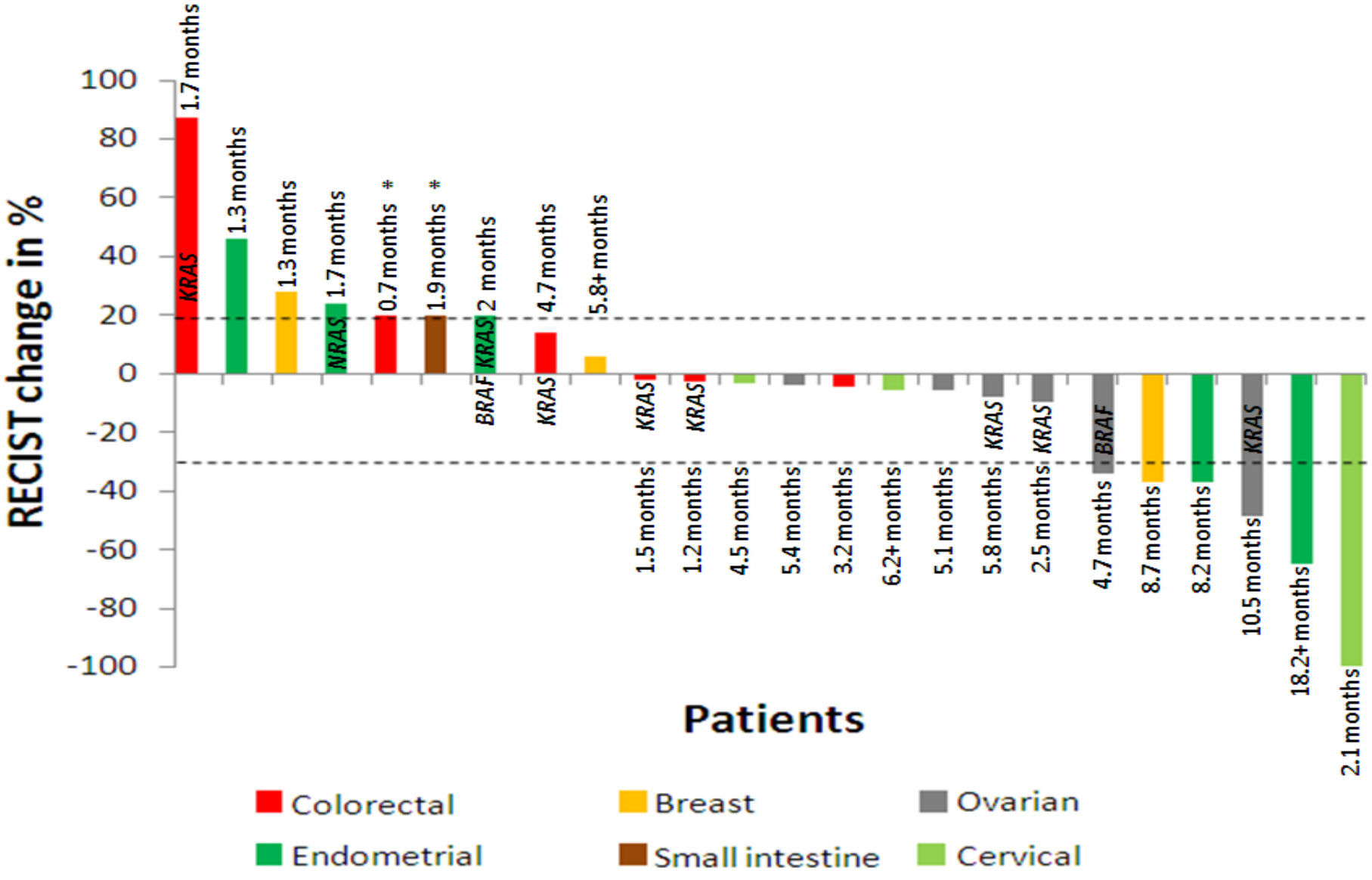
PI3K/AKT/mTOR Pathway



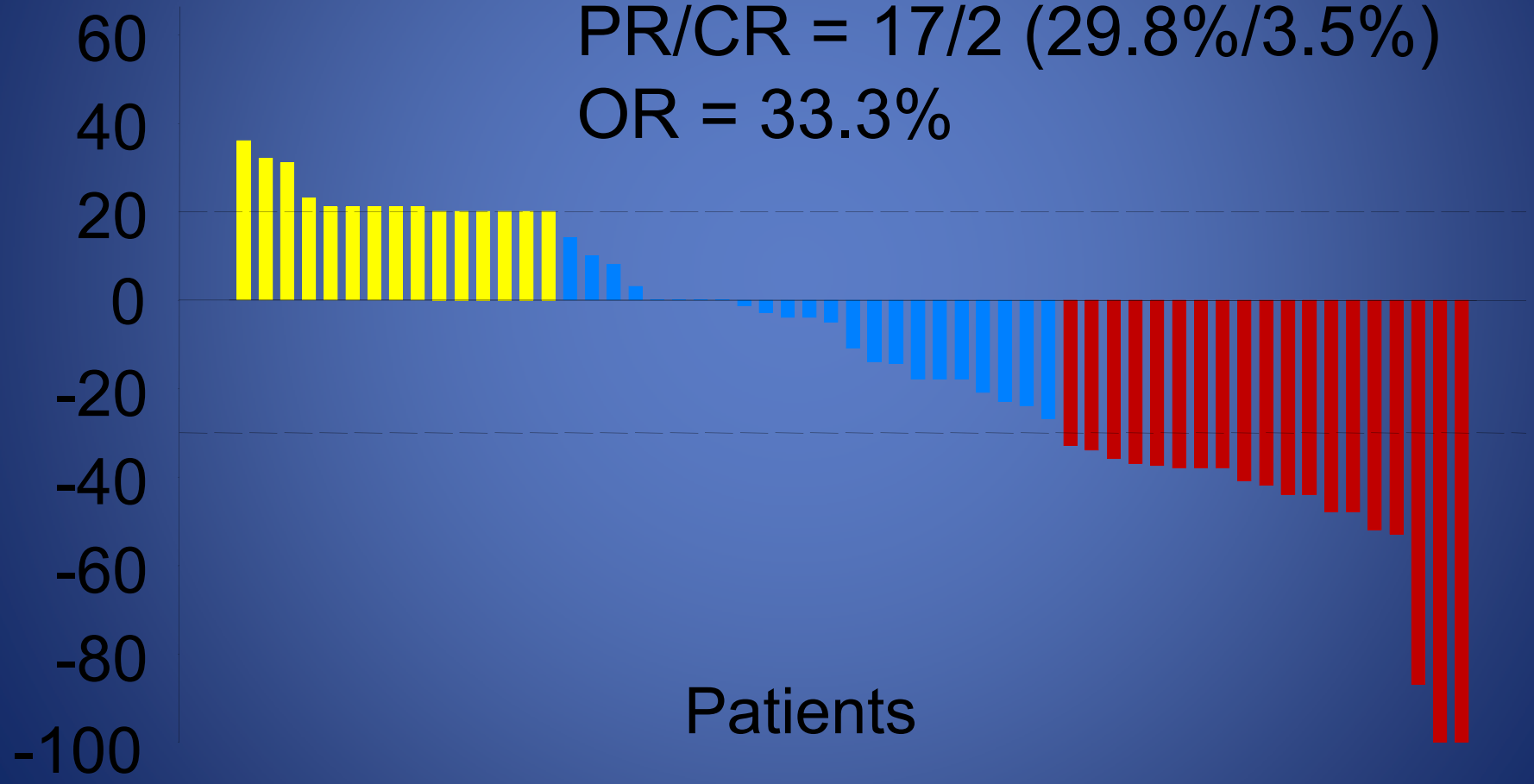
TREATED PATIENTS

- Of the 36 patients with *PIK3CA* mutations, 24 (67%) were enrolled in clinical trials that included a PI3K/AKT/mTOR inhibitor.
- These patients had a median of 3 prior therapies (1-12).
- Types of cancer of the 24 treated patients:
  - Bowel (N=7)
  - Ovarian (N=6)
  - Endometrial (N = 5)
  - Breast (N=3)
  - Cervix: squamous (N=3)

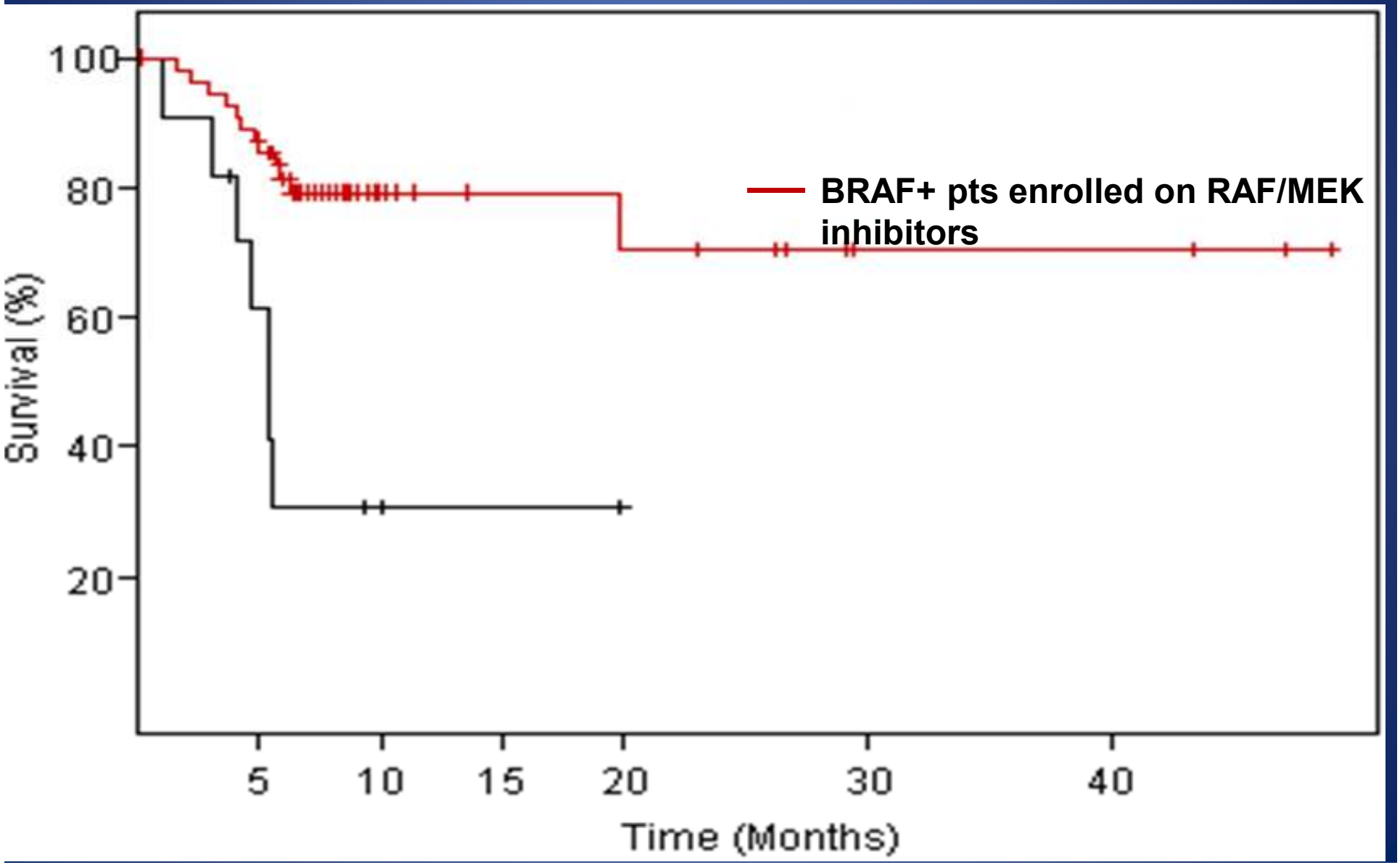
Waterfall plot of patients with *PIK3CA* mutations treated with therapies targeting the PI3K/AKT/mTOR pathway



Waterfall Plot. Response of BRAF+ Patients to BRAF or MEK Inhibitors (n=57)



Overall Survival in BRAF+ Patients. RAF/MEK vs. Other Phase I Therapies



Ongoing Phase I protocols

Protocol	Pathway Target	Current status
MLN8237 (2009-0474)	Aurora Kinase Inhibition	enrolling
MLN8237+Paclitaxel (2009-0493)	Aurora Kinase Inhibition	enrolling
ABT-348 (2009-0936)	Aurora Kinase Inhibition	enrolling
ABT-348+Gemcitabine+Carboplatin (2009-0936)	Aurora Kinase Inhibition	pending
ABT-348 +Docetaxol (2009-0936)	Aurora Kinase Inhibition	pending
Avastin+Sorafenib (2006-0638)	c-kit+VEGFR	enrolling
Dastanib+Avastin+Paclitaxel (2009-0521)	c-kit,SRC+VEGF	enrolling
Valproic Acid+Sorafenib (2007-0170)	HDAC+c-kit	enrolling
Valproic Acid+Sutent (2007-0170)	HDAC+c-kit	enrolling

Ongoing Phase I protocols

Protocol	Pathway Target	Current status
GSK2118436/GSK1120212 (2009-0949)	BRAF/MEK	enrolling
GSK1120212+Docetaxol,Erlotinib, Premetrexed, Abraxane	MEK+Chemo	pending
AZD8330 (2006-1097)	MEK	enrolling
Doxil+Velcade+Gemcitabine (2003-1002)	Proteosome inhibition+Chemo	pending
GSK1120212/GSK2141795 (2010-0122)	MEK+AKT	pending
GSK2126458 (2009-0048)	PIK3CA	enrolling
PX866 (2007-0935)	PIK3CA	enrolling
Valproic Acid+Avastin (2005-0676)	HDAC+VEGF	enrolling
CUDC-101 (2010-0483)	HDAC, EGFR, HER2	enrolling

Ongoing Phase I protocols

Protocol	Pathway Target	Current status
ABI-009 nab-rapamycin (2006-1107)	mTOR	enrolling
Avastin+Temsirolimus+Carbo(arm1) Avastin+Temsirolimus+Paclitaxel (arm2) (2010-0486)	VEGF+mTOR+Chemo	enrolling
R7112 (2007-0683)	MDM2	enrolling
Sirolimus+Cetuximab (2009-0226)	mTOR+EGFR	enrolling
Sirolimus+Docetaxol (2009-0558)	mTOR+Chemo	enrolling
Sirolimus+Vorinostat (2009-0729)	mTOR+HDAC	enrolling
Temsirolimus/Topotecan/Bortezomib (2008-0425)	mTOR+Proteosome inh+Chemo	enrolling
CVS-426	IGFR+Ang2	pending (April 2011)
BIIB-021+Imatinib	HSP90+c-kit	pending (April 2011)

- “Not only so, but we also rejoice in our sufferings, because we know that suffering produces perseverance; [4]perseverance, character; and character, hope. [5]And hope does not disappoint us” Romans 5:3-5