Le nuove "targeted therapies" in oncologia medica

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IDI

Targeted Therapies

- Do cell signaling pathways have a place in clinical practice?

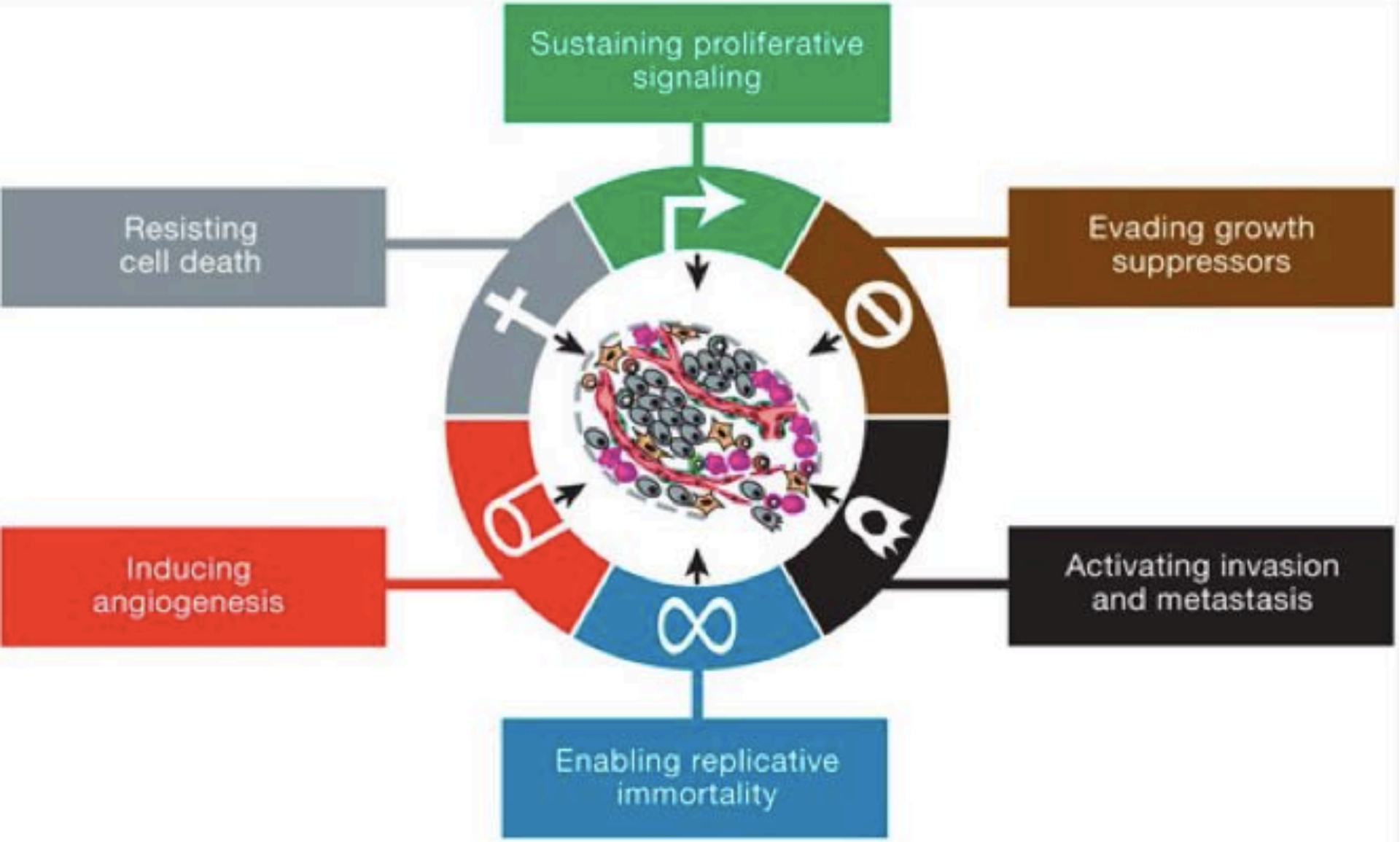
*

Targeted Therapies: The Beginning

- J. Michael Bishop and Harold E. Varmus (Nature, 1976):
  - SRC was identified as the first proto-oncogene
- Tony Hunter (PNAS, 1977)
  - SRCwas identified as a tyrosine kinase involved in cell signaling.

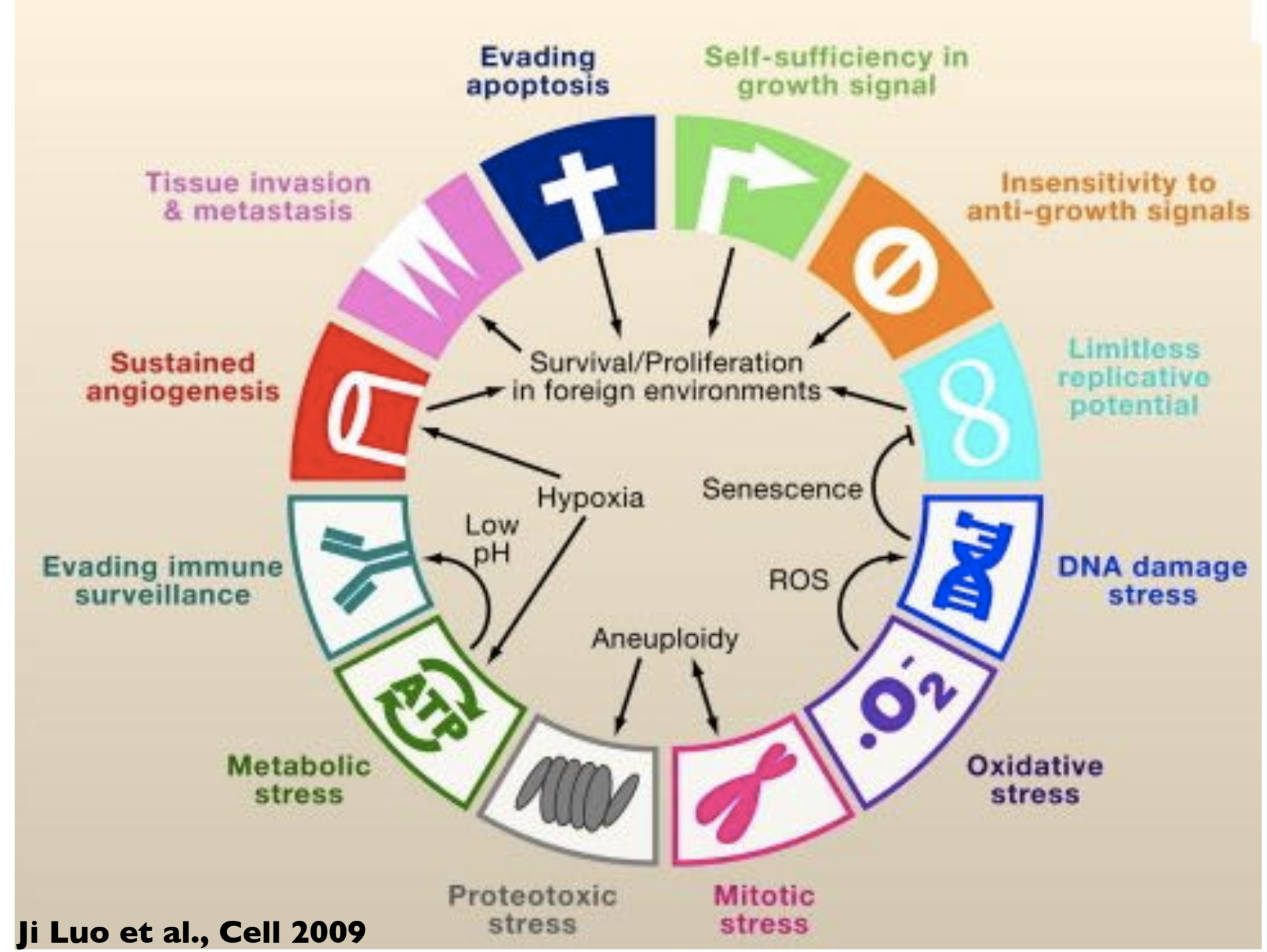
Jane de Lartigue, The International Journal of Targeted Therapies in Cancer, 2012

Anno Domini 2000

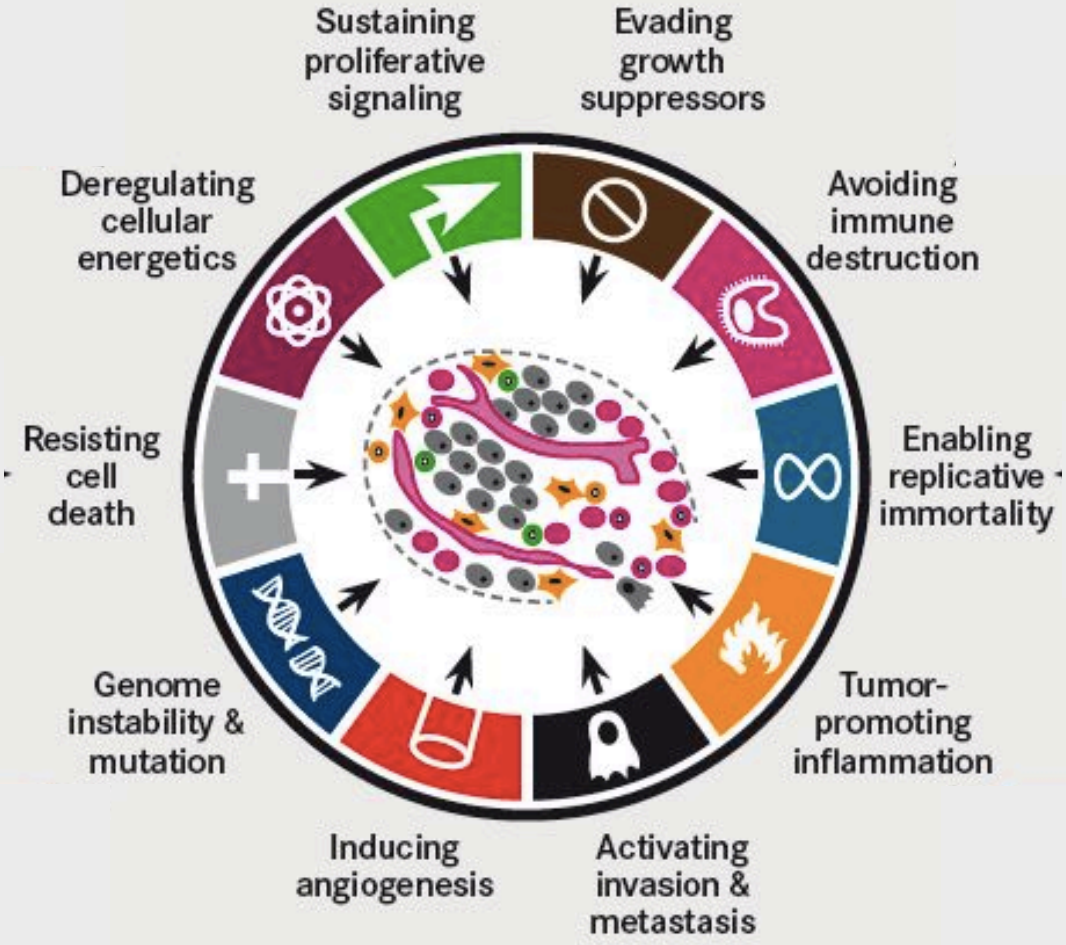


Hanahan D, Weinberg RA. Cell. 2000

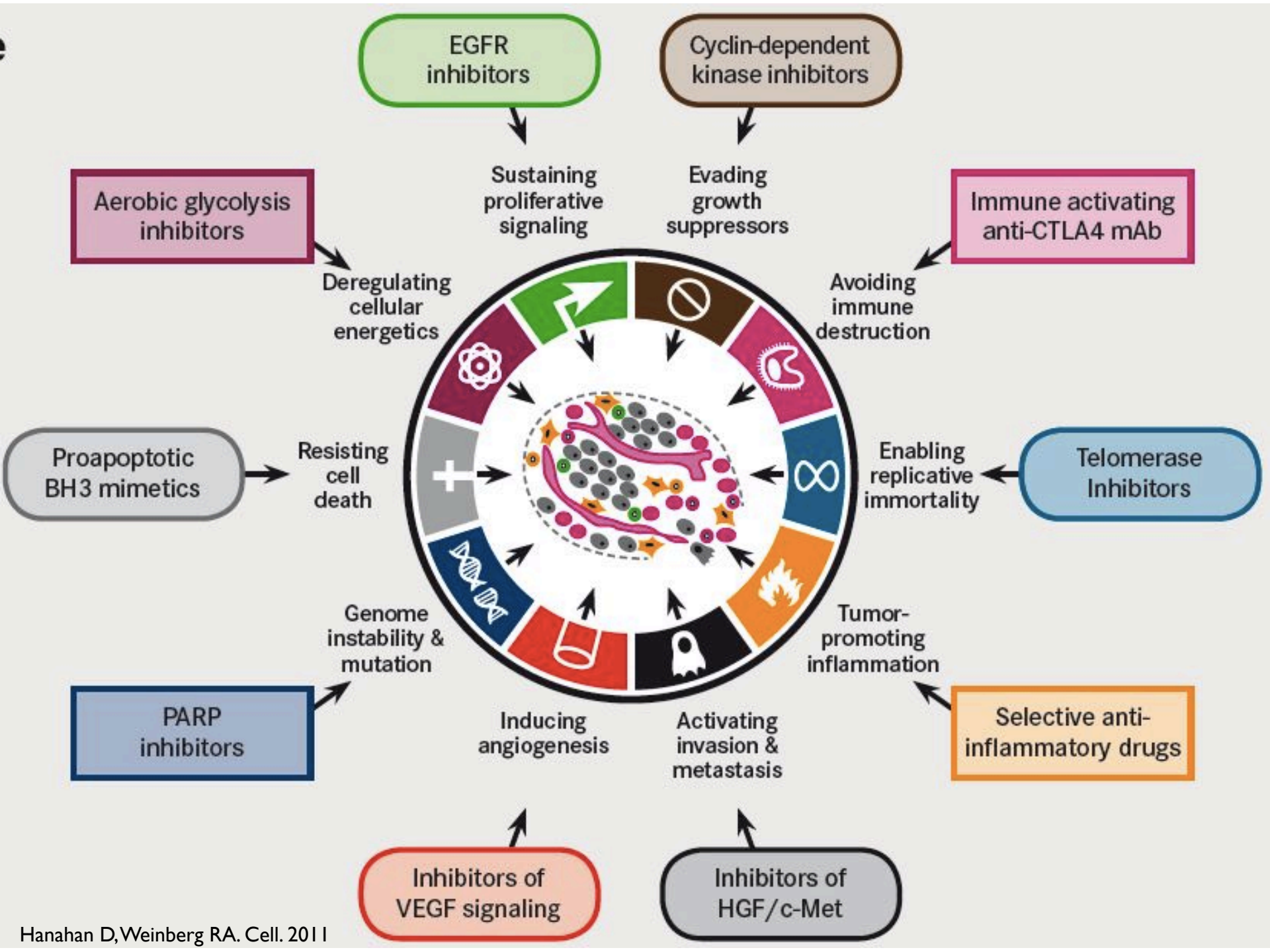

Evading apoptosis
Self-sufficiency in growth signal
Tissue invasion & metastasis
Insensitivity to anti-growth signals
Sustained angiogenesis
Survival/Proliferation in foreign environments
Limitless replicative potential



Ji Luo et al., Cell 2009



Hanahan D, Weinberg RA. Cell. 2011



Hanahan D, Weinberg RA. Cell. 2011

Cell Communication and Cancer

- Cells communicate with one another and respond to their environment predominantly by means of chemical signaling molecules that bind extracellular receptors on the surface or diffuse into the cell to bind internal receptors.
- This process stimulates a cascade of proteins that amplify signals and deliver them to intracellular destinations, where they mediate changes in cellular activity.

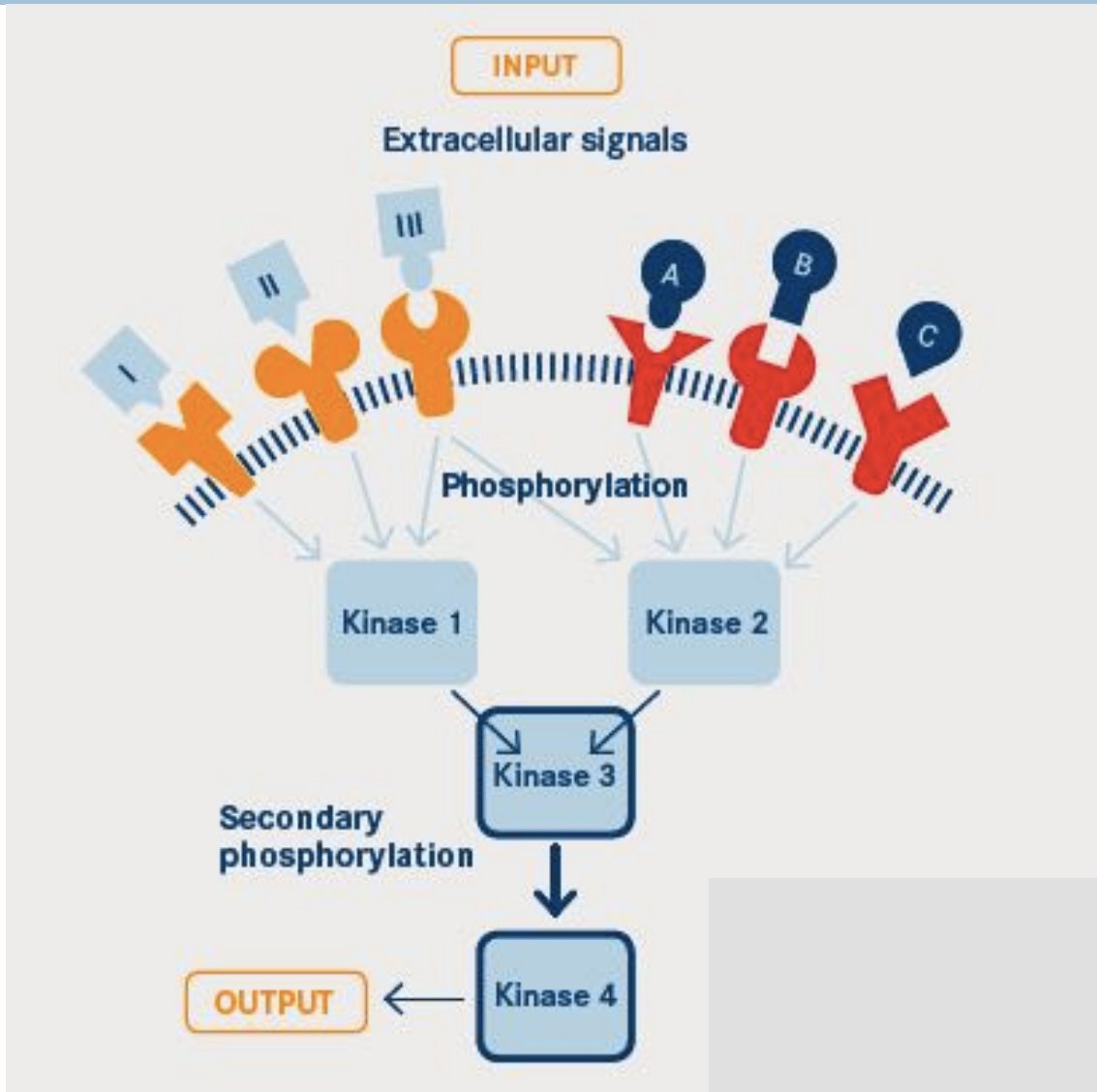
Jane de Lartigue, The International Journal of Targeted Therapies in Cancer, 2012

Tyrosine Kinases and Cancer

- As key regulators of proliferation and growth, more than 30 RTKs have been implicated in cancer, as have the 2 main signaling pathways that they regulate
  - the mitogen-activated protein kinase (MAPK) pathway
  - the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathway

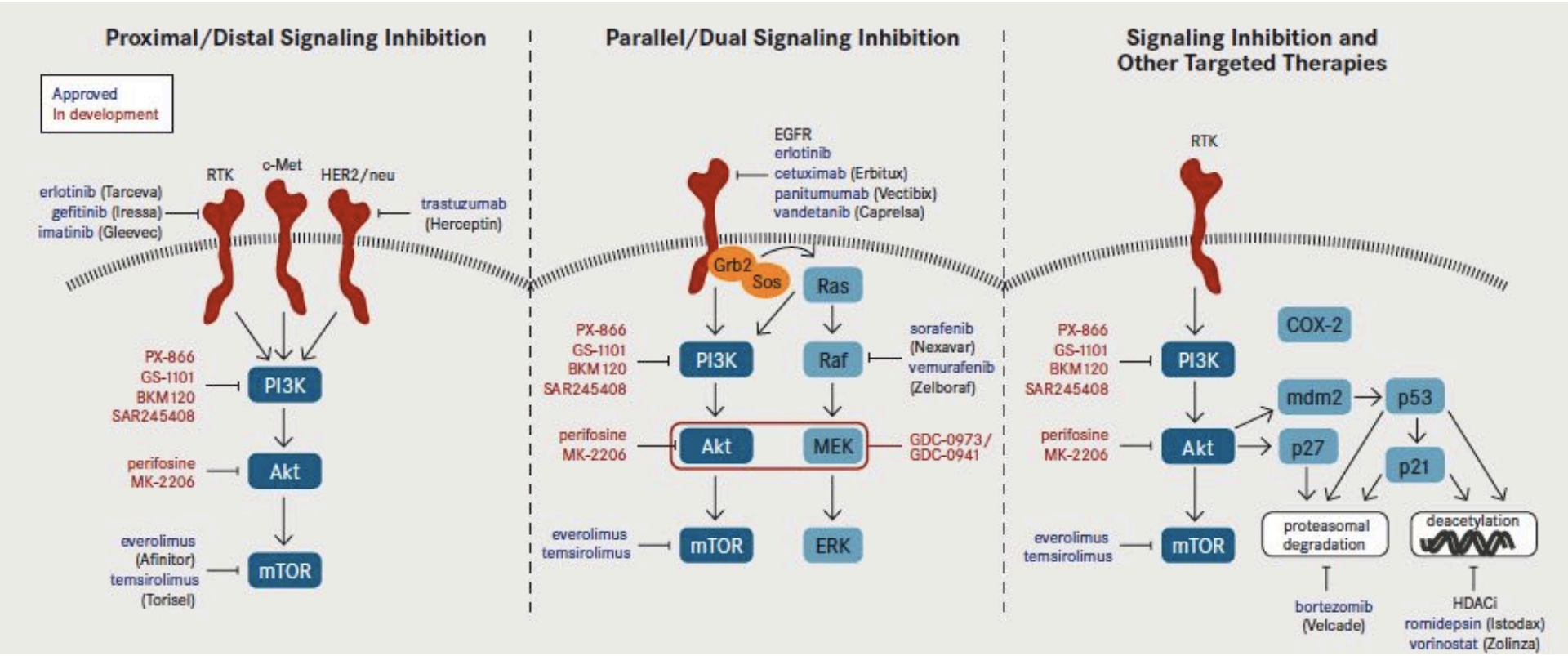
Jane de Lartigue, The International Journal of Targeted Therapies in Cancer, 2012

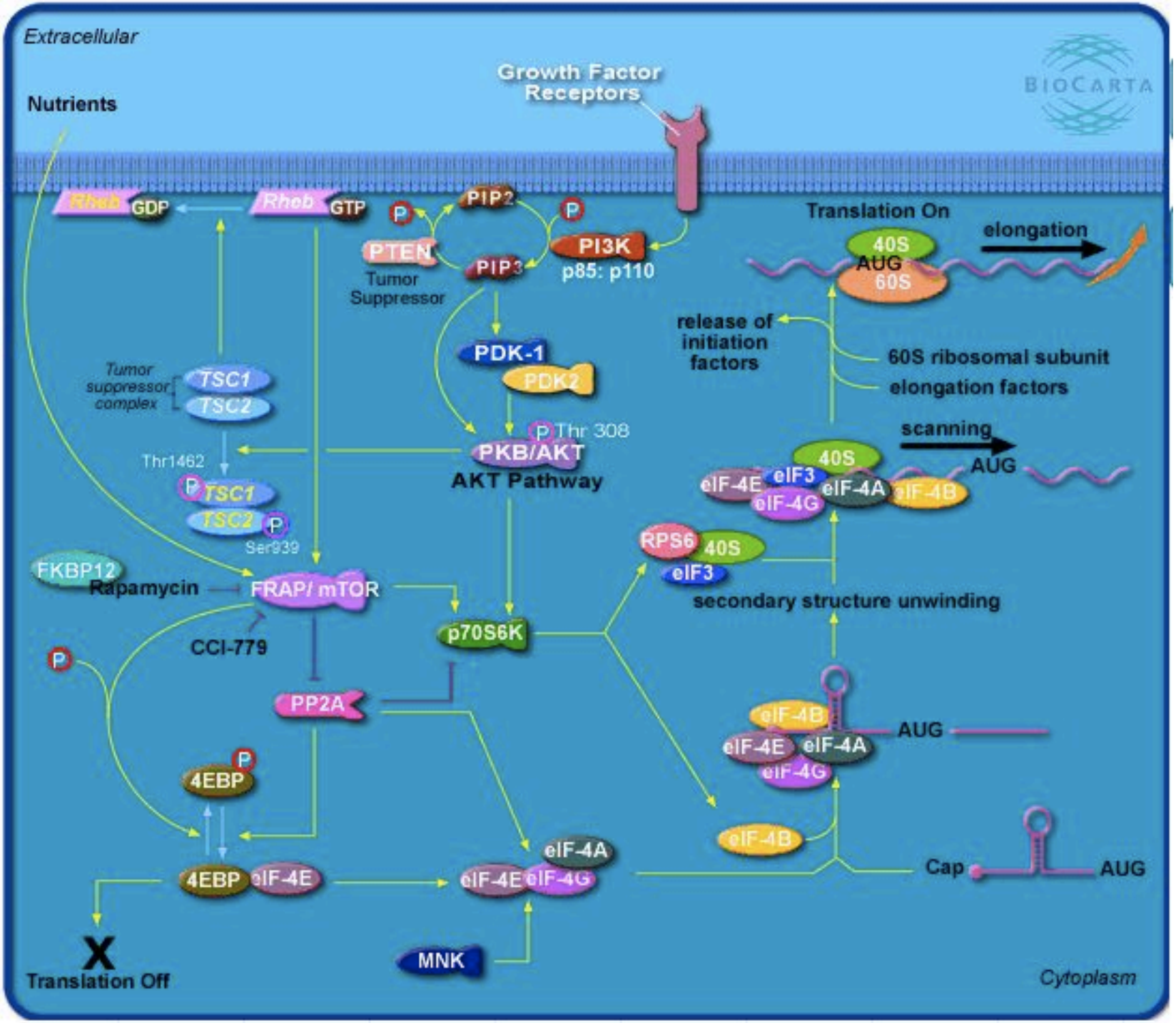
Signal reception activates cascade



Jane Wang,

The Science Creative Quarterly, 2003

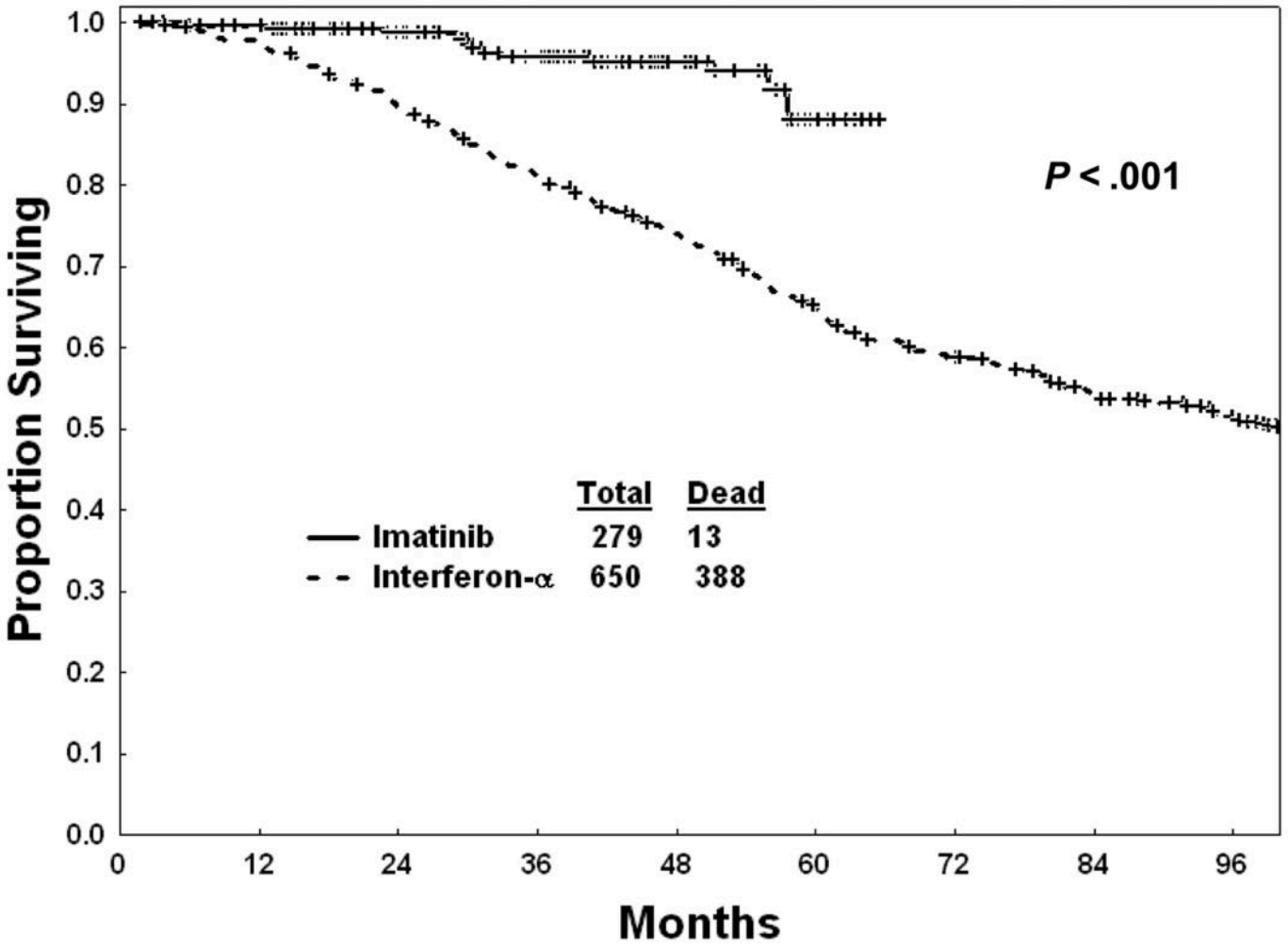

Proximal/Distal Signaling Inhibition
Approved
In development
RTK
c-Met
HER2/neu
erlotinib (Tarceva)
gefitinib (Iressa)
imatinib (Gleevec)
trastuzumab
(Herceptin)
PX-866
GS-1101
BKM120
SAR245408
PI3K
perifosine
MK-2206
Akt
everolimus
(Afinitor)
temsirolimus
(Torisel)
mTOR
Parallel/Dual Signaling Inhibition
EGFR
erlotinib
cetuximab (Erbitux)
panitumumab (Vectibix)
vandetanib (Caprelsa)
Grb2
Sos
Ras
PX-866
GS-1101
BKM120
SAR245408
PI3K
Raf
sorafenib
(Nexavar)
vemurafenib
(Zelboraf)
perifosine
MK-2206
Akt
MEK
GDC-0973/
GDC-0941
everolimus
temsirolimus
mTOR
ERK
Signaling Inhibition and
Other Targeted Therapies
RTK
PX-866
GS-1101
BKM120
SAR245408
PI3K
COX-2
mdm2
p53
perifosine
MK-2206
Akt
p27
p21
everolimus
temsirolimus
mTOR
proteasomal
degradation
deacetylation
bortezomib
(Velcade)
HDACi
romidepsin (Istodax)
vorinostat (Zolinza)


Extracellular
Nutrients
Growth Factor Receptors
BIOCARTA
Rheb GDP
Rheb GTP
PIP2
PIP3
PTEN
Tumor Suppressor
PI3K
p85: p110
Translation On
40S
AUG
60S
elongation
release of initiation factors
60S ribosomal subunit
elongation factors
PDK-1
PDK2
Tumor suppressor complex
TSC1
TSC2
Thr 308
PKB/AKT
AKT Pathway
Thr1462
Ser939
scanning
AUG
eIF-4E
eIF3
eIF-4A
eIF-4B
eIF-4G
RPS6
FKBP12
Rapamycin
FRAP/ mTOR
CCI-779
p70S6K
secondary structure unwinding
PP2A
4EBP
Cap
Translation Off
MNK
Cytoplasm

~15 Years Later –How Have We Done?
Have our predictions/assumptions proved correct?

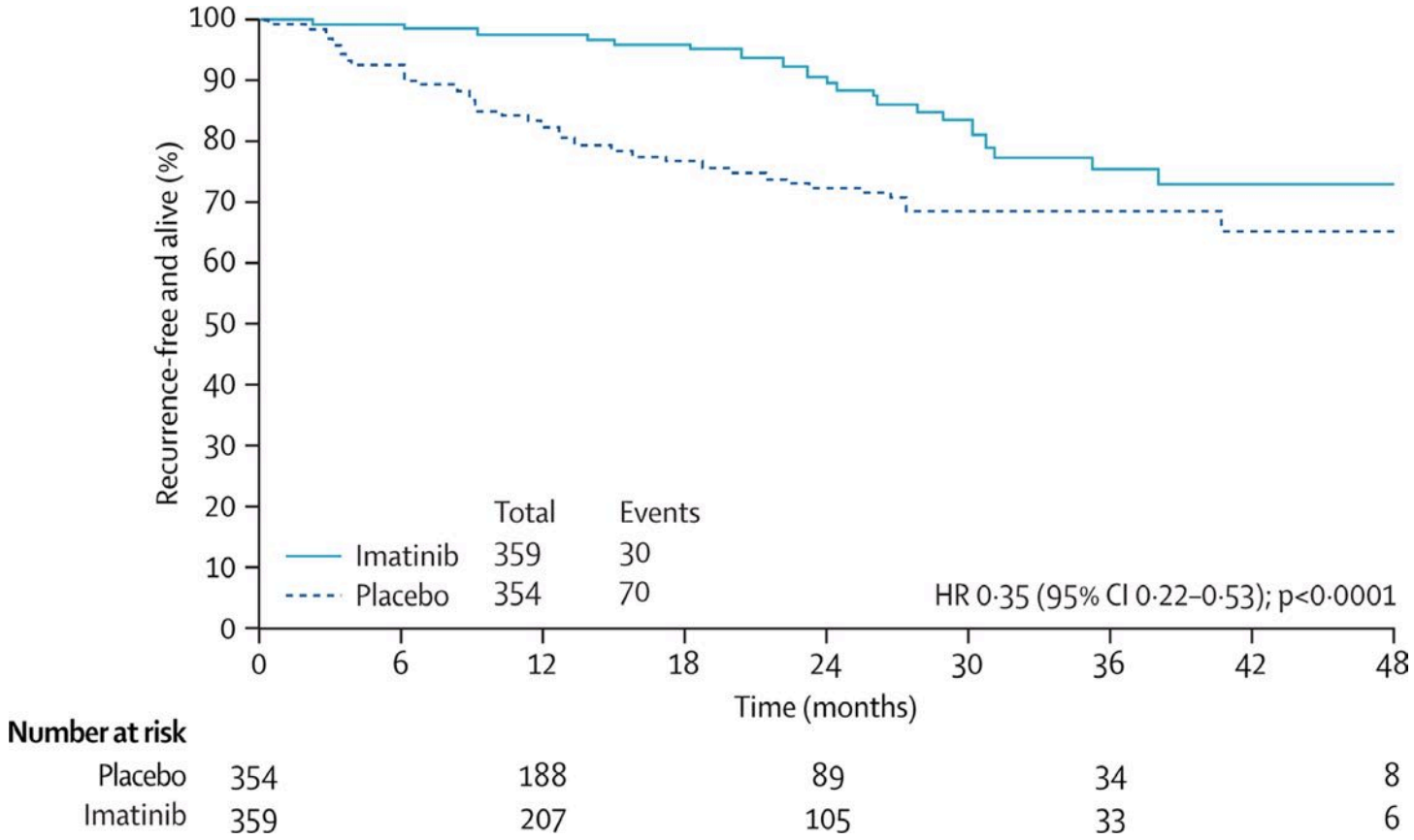
- Mixed Reviews on Efficacy:
  - Some very exciting: major gains, transforming disease outcomes.

Chronic Myeloid Leukemia Overall Survival: Imatinib Mesylate vs. Interferon-alpha



Kantarjian, H. M. et al. Blood 2006;108:1835-1840

GI Stromal Tumour: Recurrence Free Survival Imatinib Mesylate vs. Placebo



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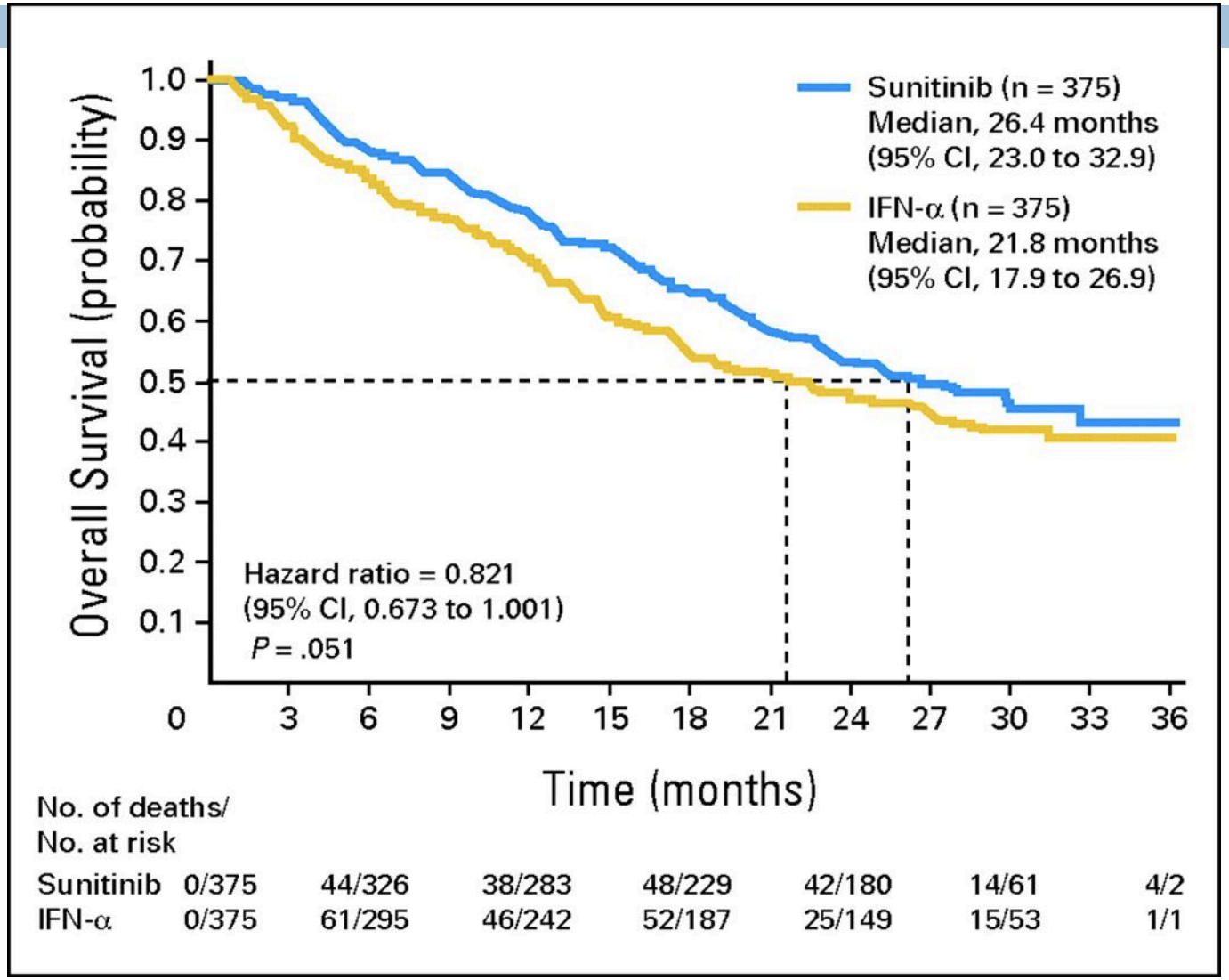
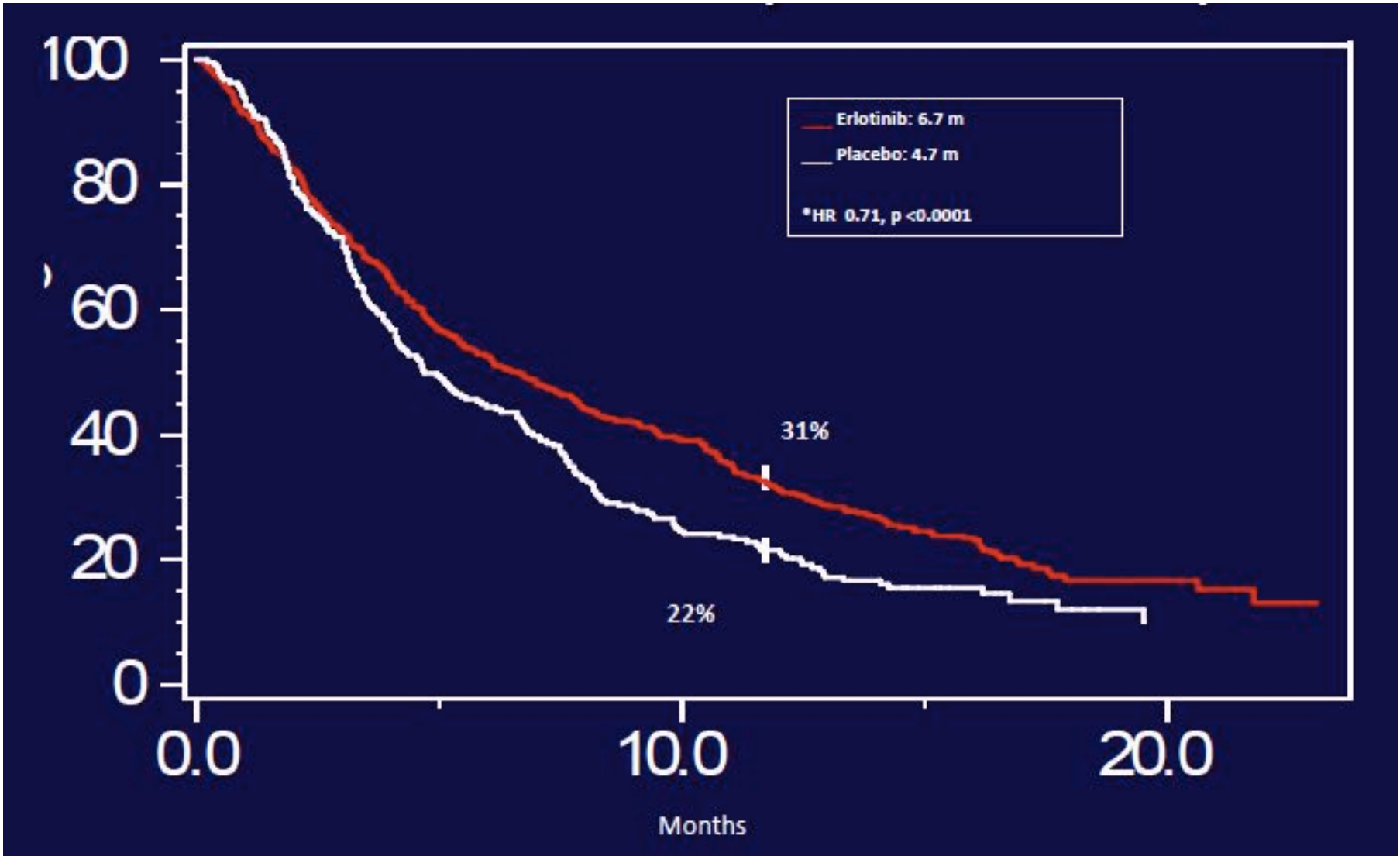
  - Some modest -- but still practice changing

Renal Cell Carcinoma: Overall Survival Sunitinib vs. IFN alpha

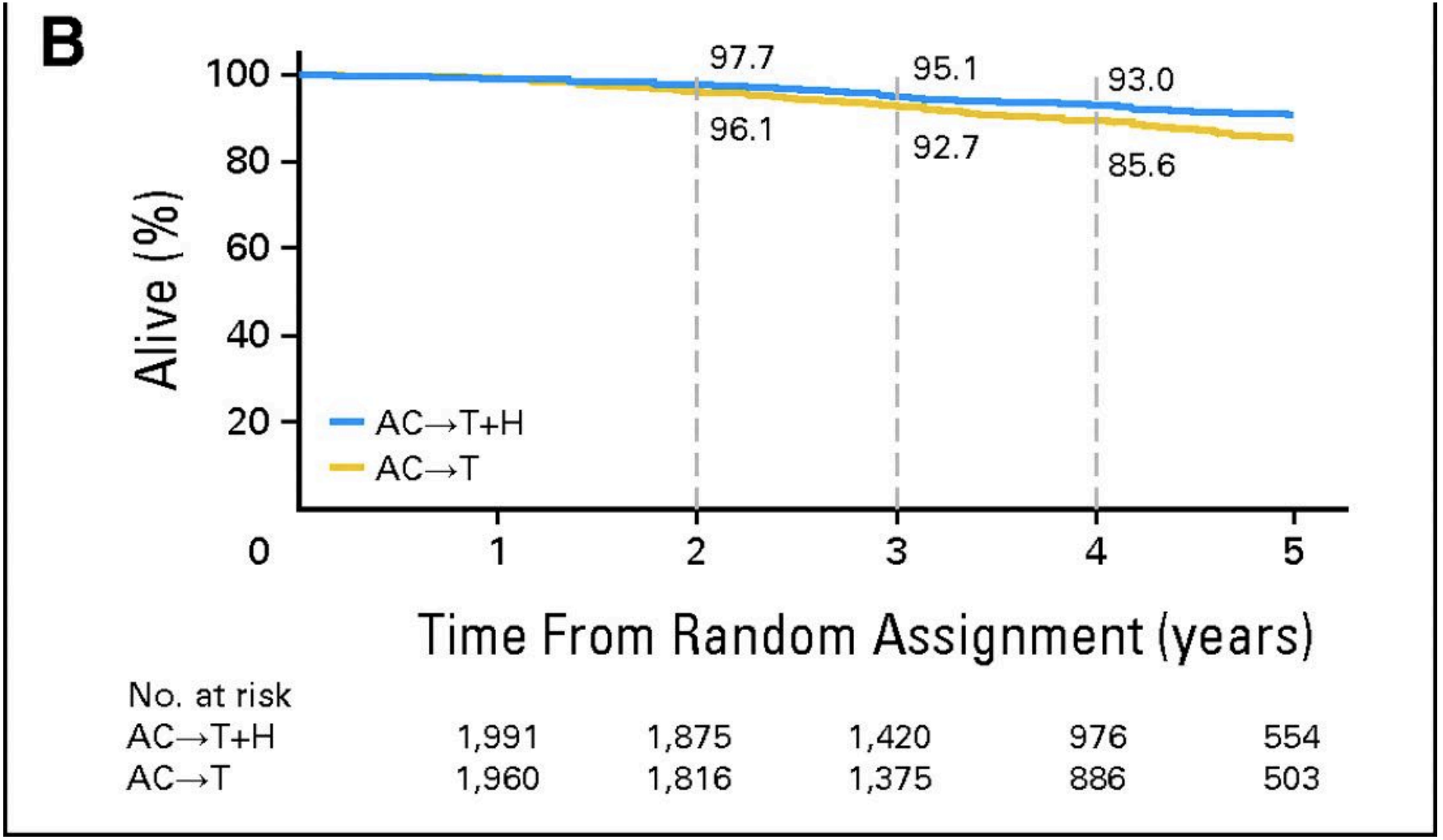


Motzer R J et al. JCO 2009;27:3584-3590

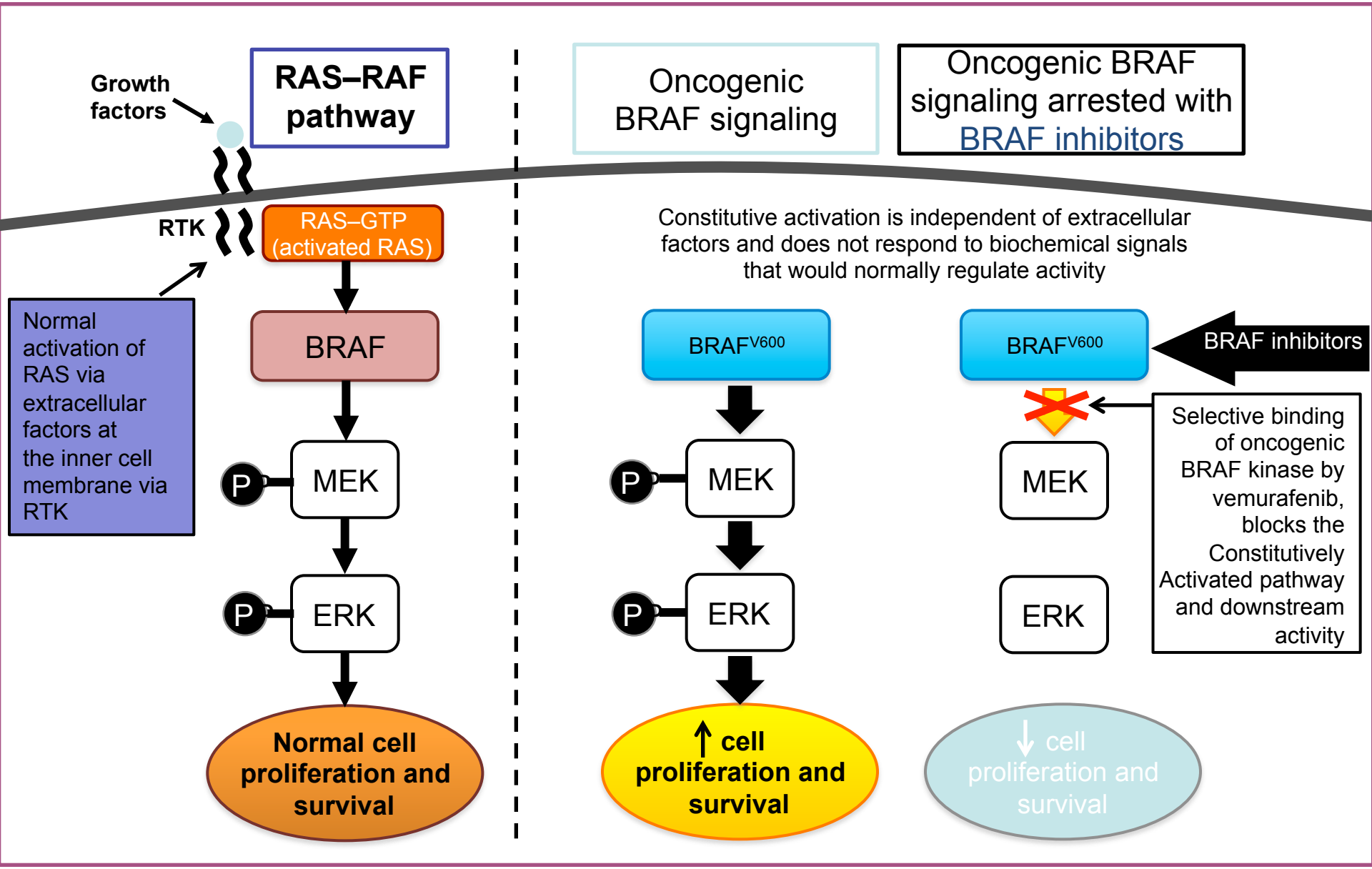
Erlotinib NSCLC Results:Erlotinib vs. Placebo (NCIC CTG BR.21)



Adjuvant Trastuzumabin HER2 Positive Breast Cancer – Overall Survival

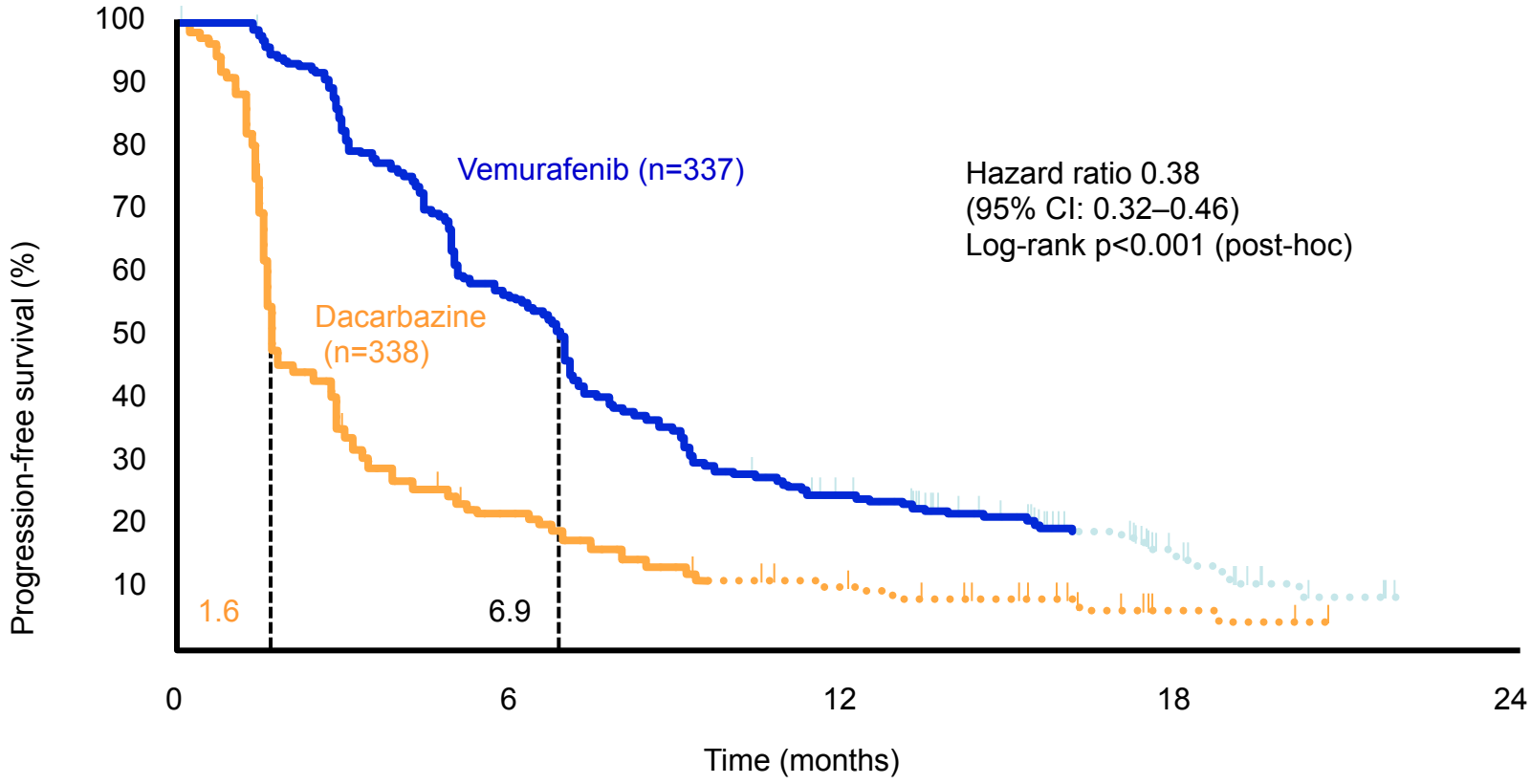


Perez E A et al. JCO 2011;29:3366-3373



Ascierto PA. et al. J Trans Med. 2012 May 3;10(1):85.

Progression-free survival (February 01, 2012 cut-off) censored at crossover

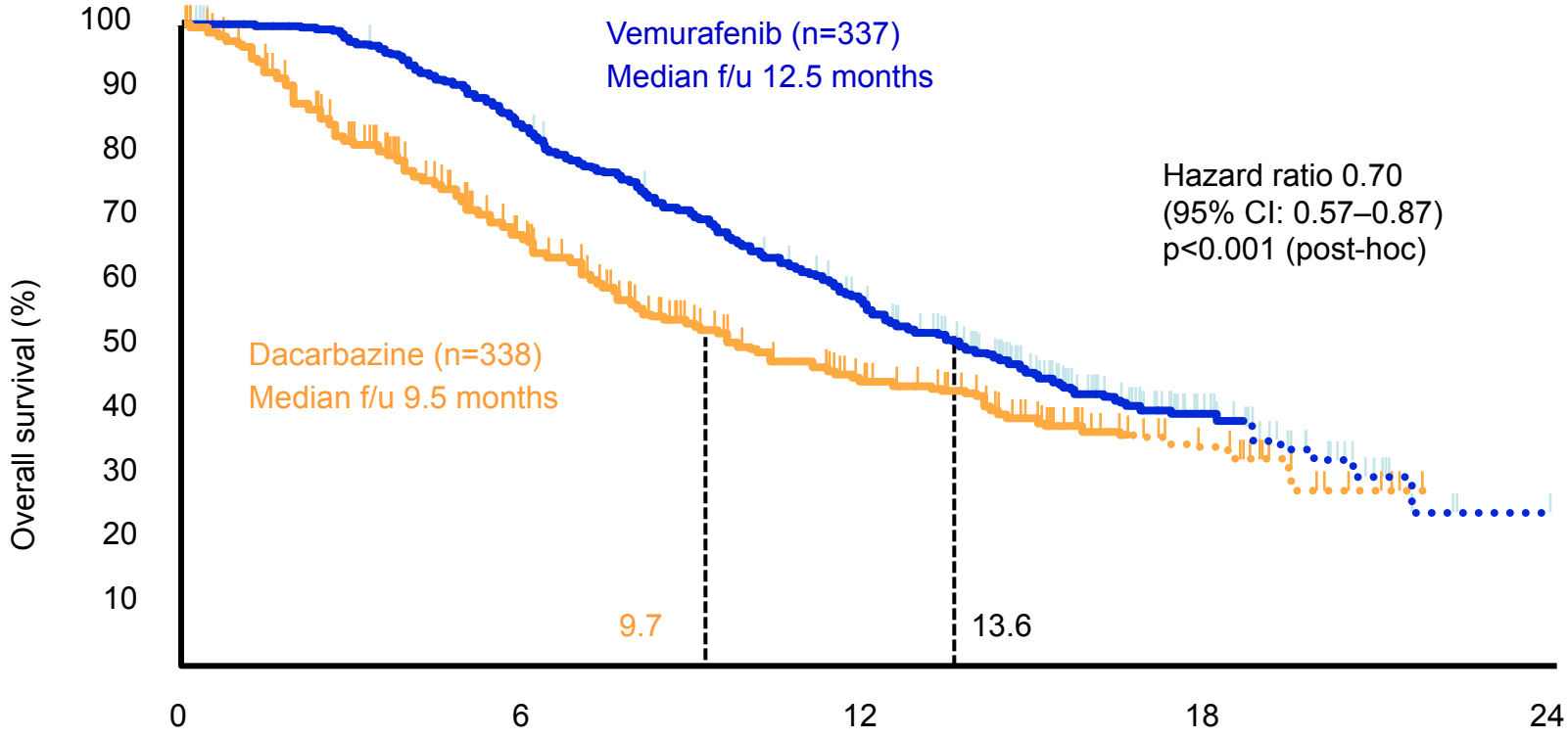


No. at risk

Dacarbazine	338	100	63	37	22	14	3	0	0
Vemurafenib	337	269	186	113	77	49	16	3	0

Chapman P. et al. abs 8502 ASCO Ann. Meeting Chicago 2012

Overall survival (February 01, 2012 cut-off) censored at crossover

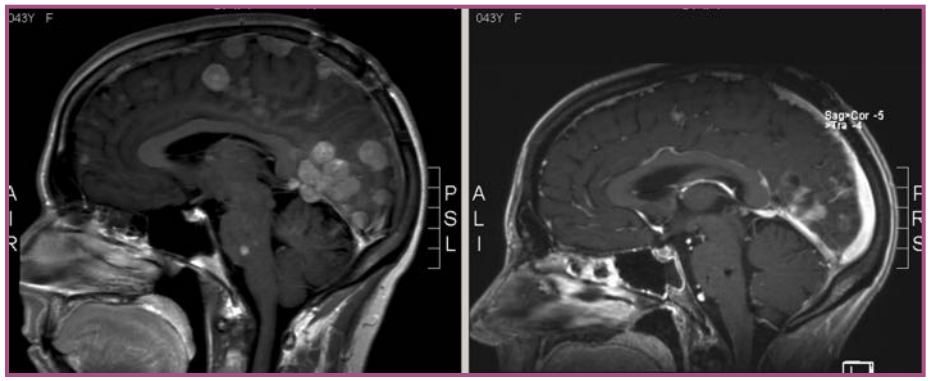


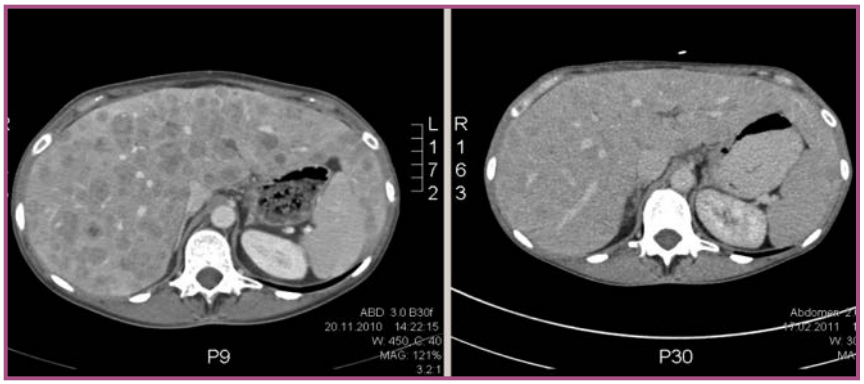
No. at risk									
Dacarbazine	338	244	173	111	79	50	24	4	0
Vemurafenib	337	326	280	231	178	109	44	7	1

Chapman P. et al. abs 8502 ASCO Ann. Meeting Chicago 2012

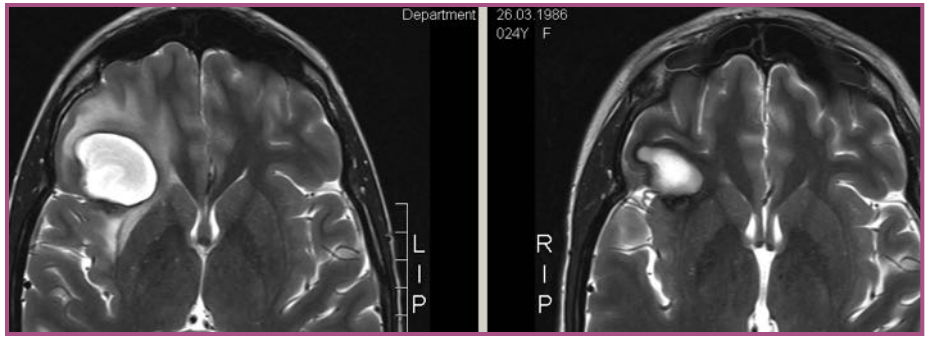
Results: Efficacy[1]

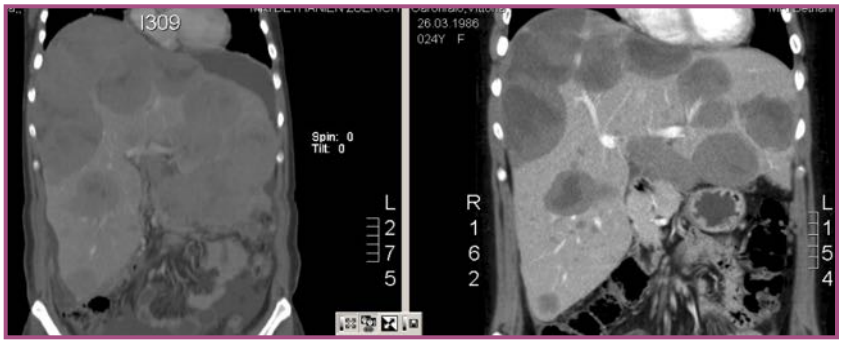
Patient 1: partial response in brain and liver





Patient 2: minor response confirmed by brain MRI and regression of liver metastases





Dummer R, et al. Poster presentation at ASCO 2011. J Clin Oncol 29: 2011 (suppl; abstr 8548).

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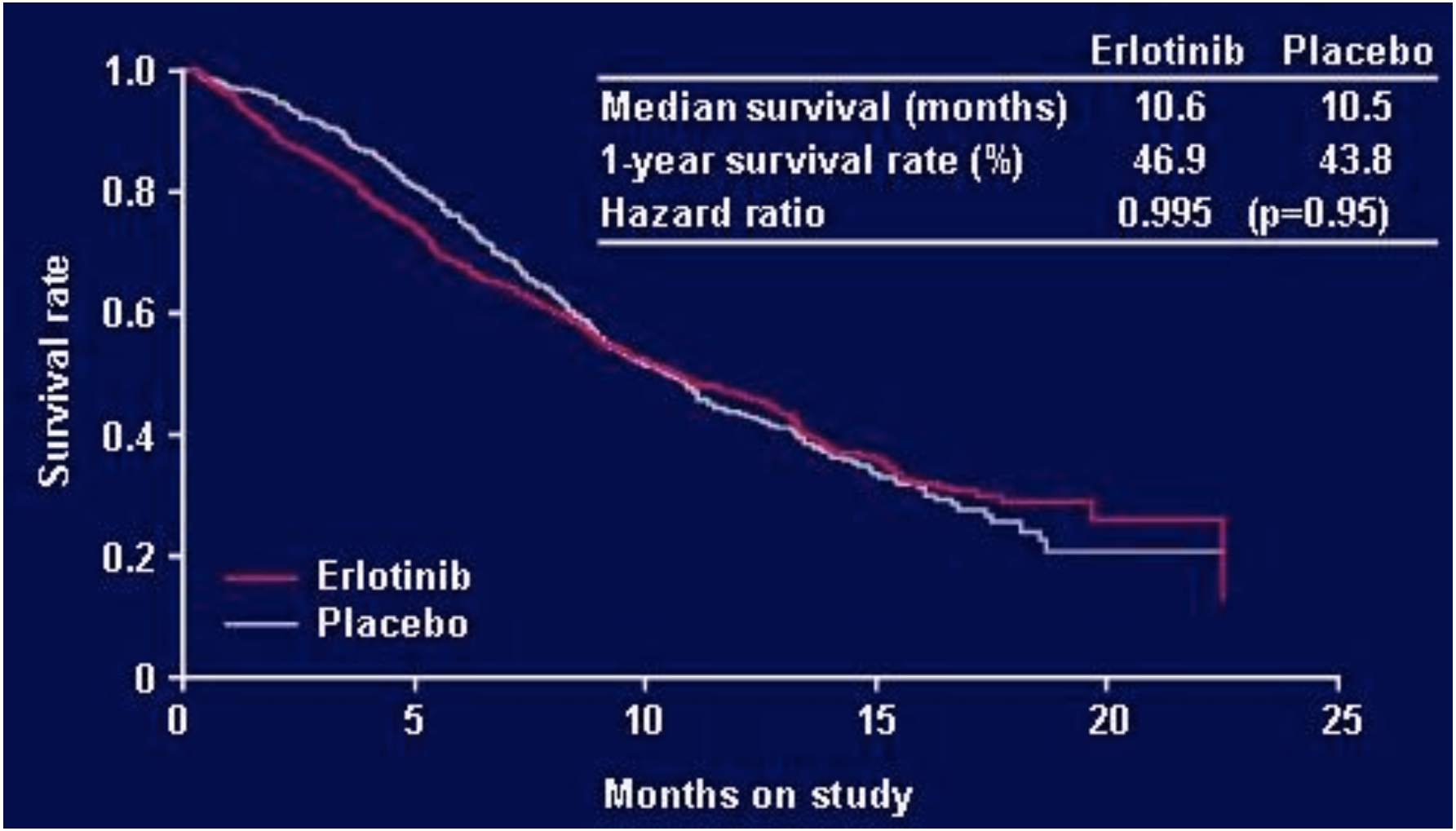
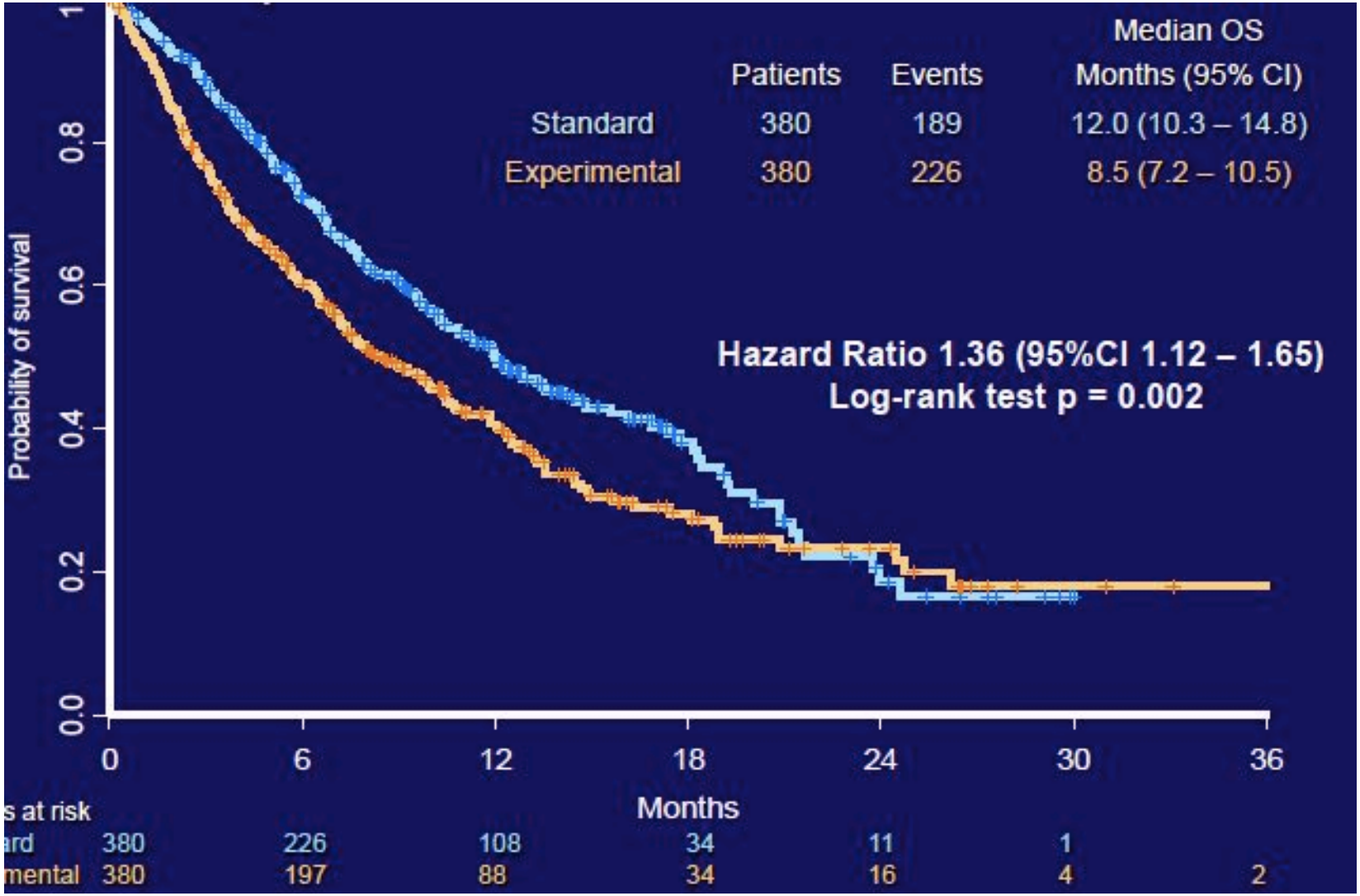
  - Many others negative -- or worse

Erlotinib NSCLC Results: TRIBUTE trial of Combination chemotherapy +/−Erlotinib



NSCLC Overall Survival:
Standard: Chemo ⇨ Erlotinib
Experimental: Erlotinib ⇨ Chemo



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  - What are the adjuvant results of FDA approved targeted agents?

What are the adjuvant results of FDA approved targeted agents?

Target	*Agent*	*Approved advanced disease indication*	*Adjuvant - status?*
mTOR	everolimus	Renal	1 trial ongoing
		Panc. Neuroend.	?
	temsirolimus	Renal	?
VEGF/ VEGFR	bevacizumab	Colorectal	**2 trials negative (CO-8, AVANT)**
		Lung	1 trial not reported (E1505)
		Renal	-
		Brain	2 trials in GBM- not reported
		~~Breast~~	Several trials not reported
	sunitinib	Renal	3 trials - ongoing
		Panc. Neuroend.	?
		GIST	?
	sorafenib	Renal	3 trials - ongoing
		Hepatocellular	1 trial not reported
	pazopanib	Renal	1 Trial - ongoing
	vandetanib	Thyroid	?
	axitinib	Renal	?

What are the adjuvant results of FDA approved targeted agents?

Target	*Agent*	*Approved advanced disease indication*	*Adjuvant - status?*
HER2	trastuzumab	Breast	**Trials positive for RFS/OS**
		Gastric	?
	lapatinib	Breast	1 trial (ALTTO) not reported
EGFR	panitumumab	Colorectal	1 trial in rectal ongoing
	cetuximab	Colorectal	**1 trial – negative in RAS WT;** ***worse outcome in RAS mut***
		Head and Neck	1 trial (RTOG 0920) ongoing
	erlotinib	NSCLC	1 trial (RADIANT) not reported 2 trials ongoing
		Pancreas	2 trials ongoing
	gefitinib	NSCLC	**2 trials negative (BR19, S0023)** ***(gefitinib arm - worse outcome)*** 1 trial recruiting in EGFR mut
Kit	imatinib	GIST	**Trials positive for RFS & OS**
BRAF	vemurafenib	Melanoma	planned
EML4-ALK	crizotinib	NSCLC	?

Summary Targeted Therapies –To Date: Toxicity and Efficacy in Common Solid Tumours

- **Efficacy**:
  - Advanced disease survival –some positive, mostly modest
  - Effects on long term survival (adjuvant) –with exception of trastuzumab and imatinib, so far all are negative
- **Toxicity**:
  - Common adverse effects of cytotoxics (hematological, hair loss) not generally seen
  - Newtypes of adverse effects, some of which affect patient QoL: skin rash, fatigue, hypertension

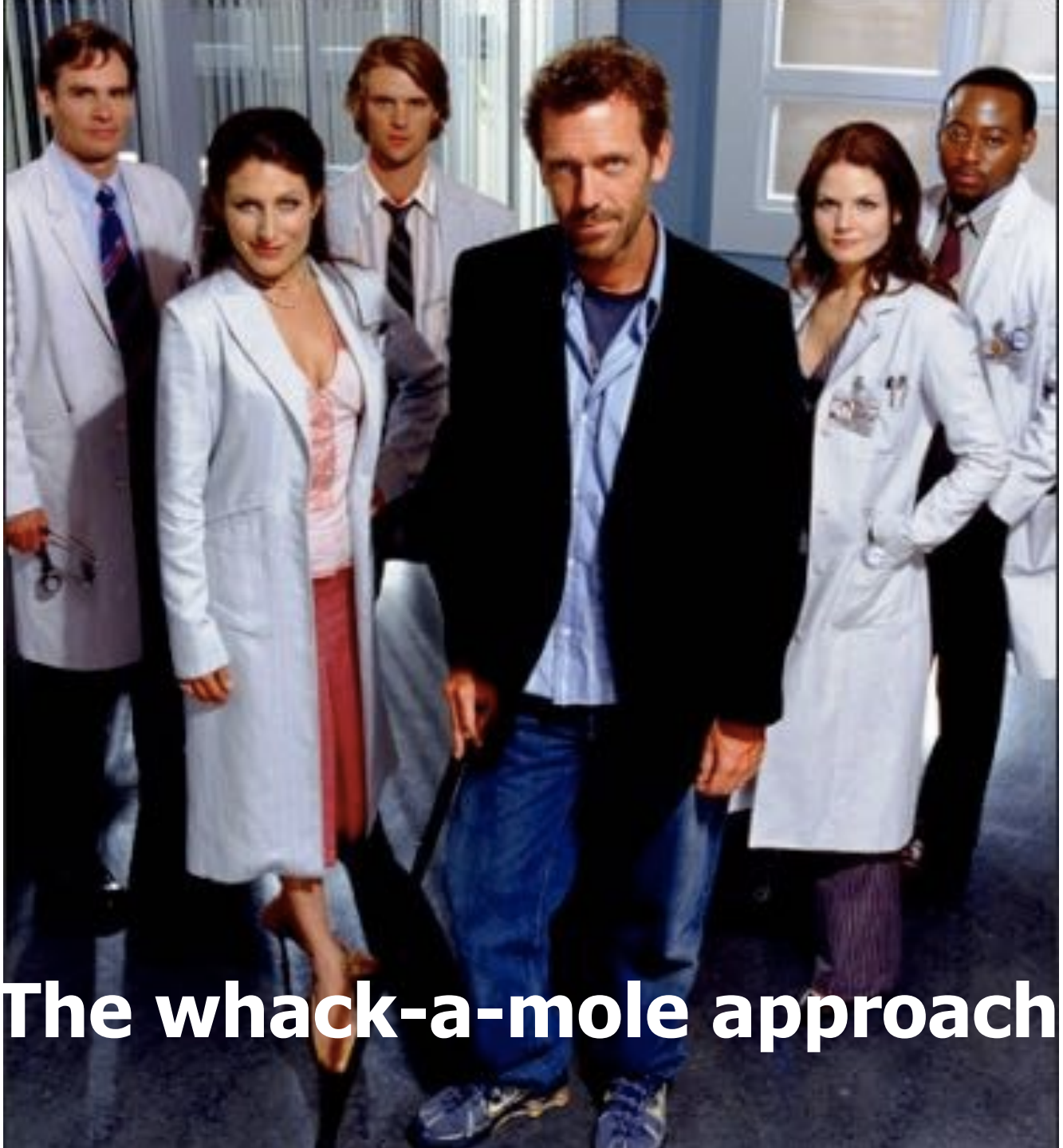
How can we improve outcomes going forward?

- Potential Issues
  - Targets tackled
  - Agents and their dosing
  - Patient/tumour selection
  - Trial design
  - Drug resistance
  - The race to be “first” to market
  - Cost containement

Cell Communication and Cancer

- *Current thinking suggests that the model of linear cell signaling pathways should be replaced by one incorporating large, complex signaling networks in which cancer genes are often enriched in signaling "hubs."*

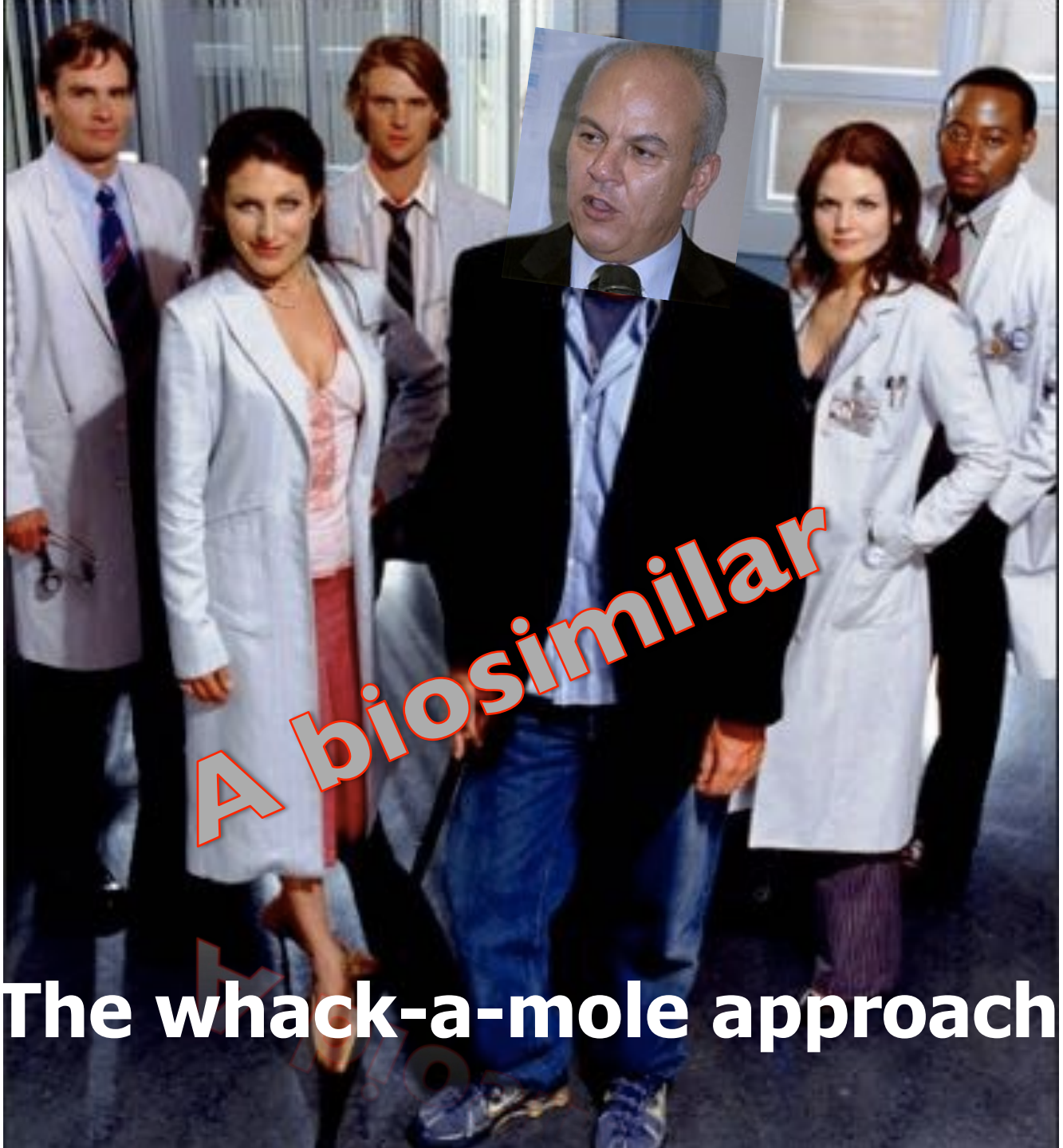
Jane de Lartigue, The International Journal of Targeted Therapies in Cancer, 2012



The whack-a-mole approach

Source: Flickr

The whack-a-mole game

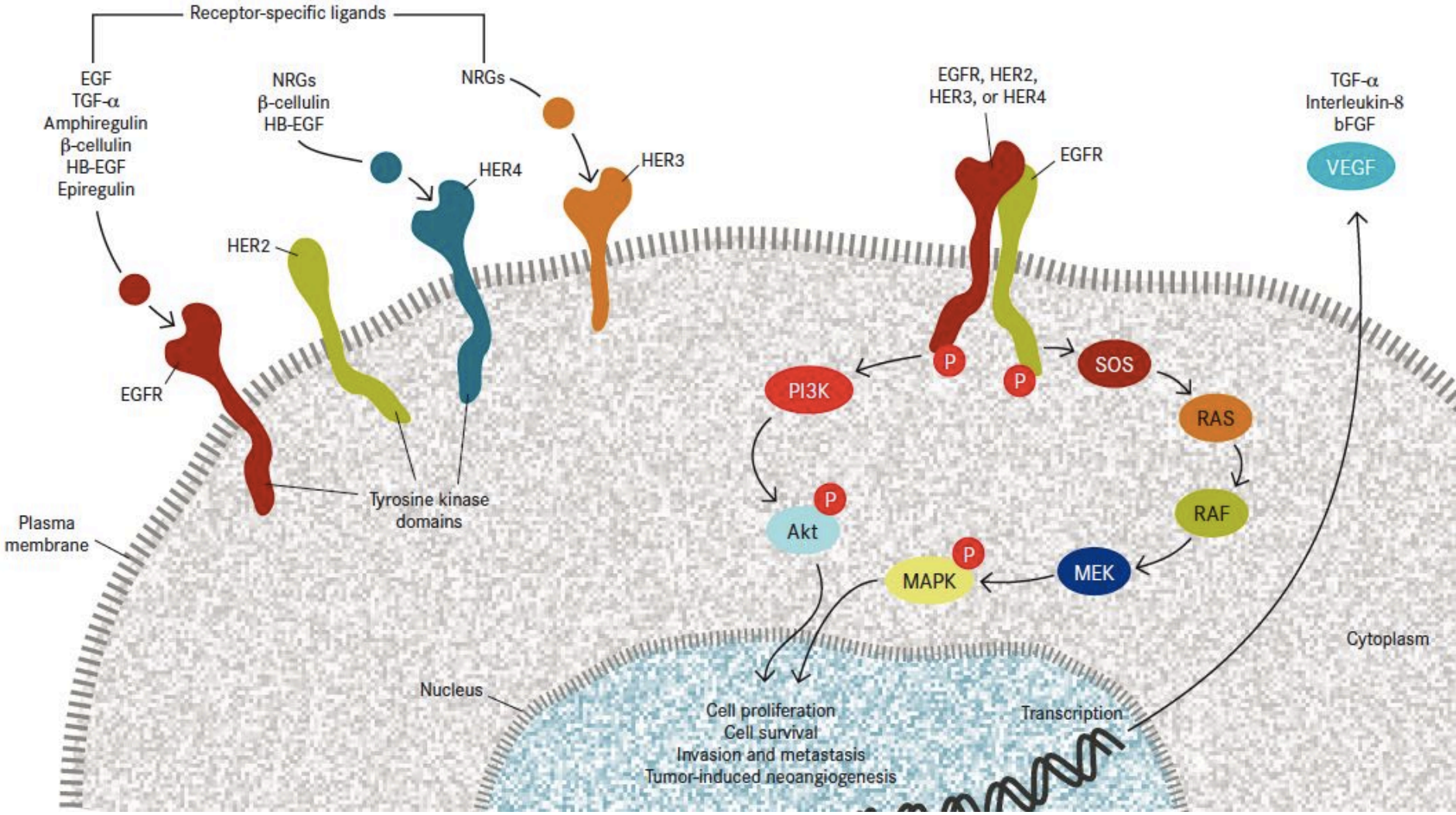


The whack-a-mole approach

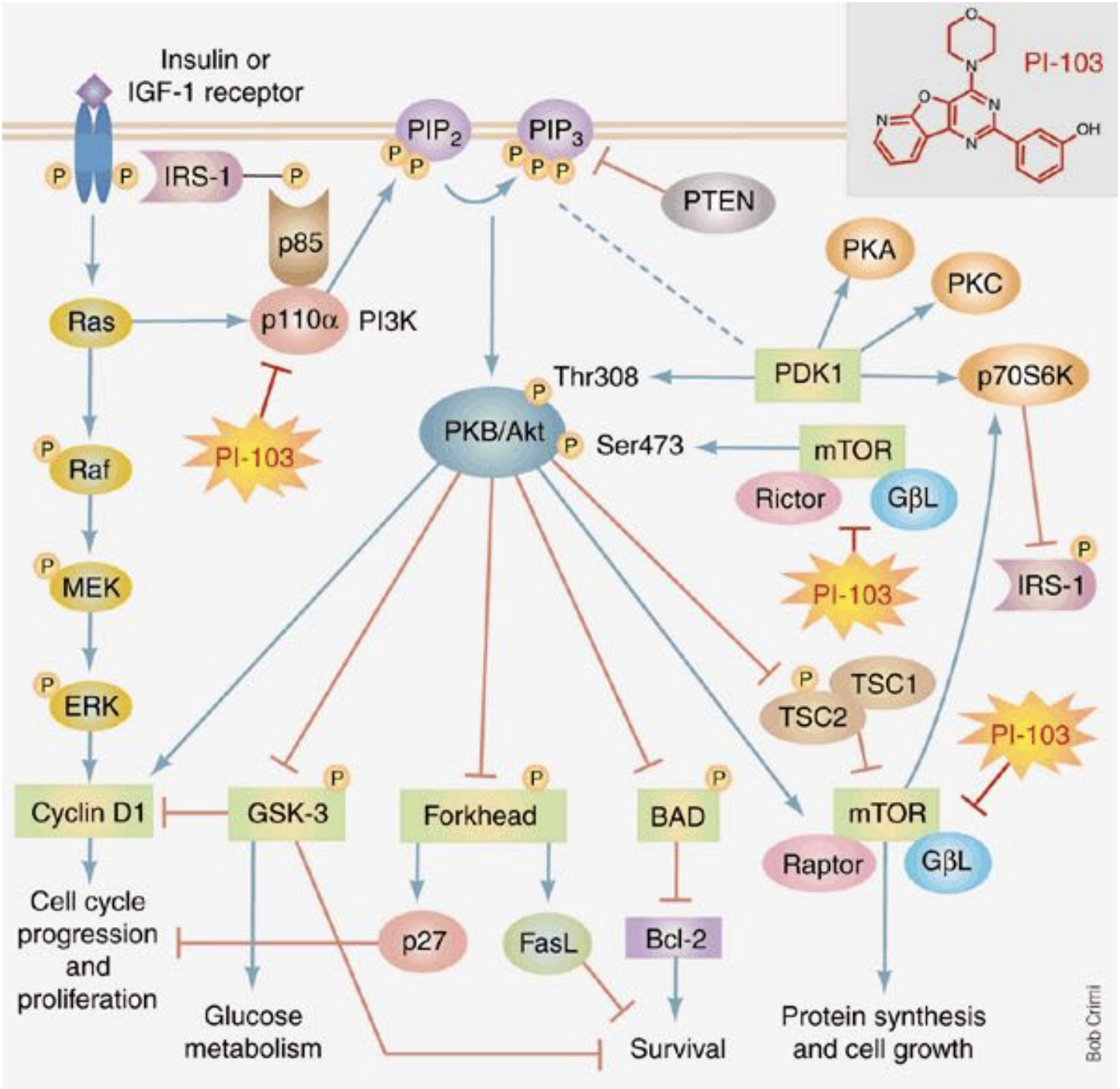
Source: Flickr

The whack-a-mole approach

When Targeted Therapies Don't Work




EVERY TUMOR
HAS AN ESCAPE PLAN

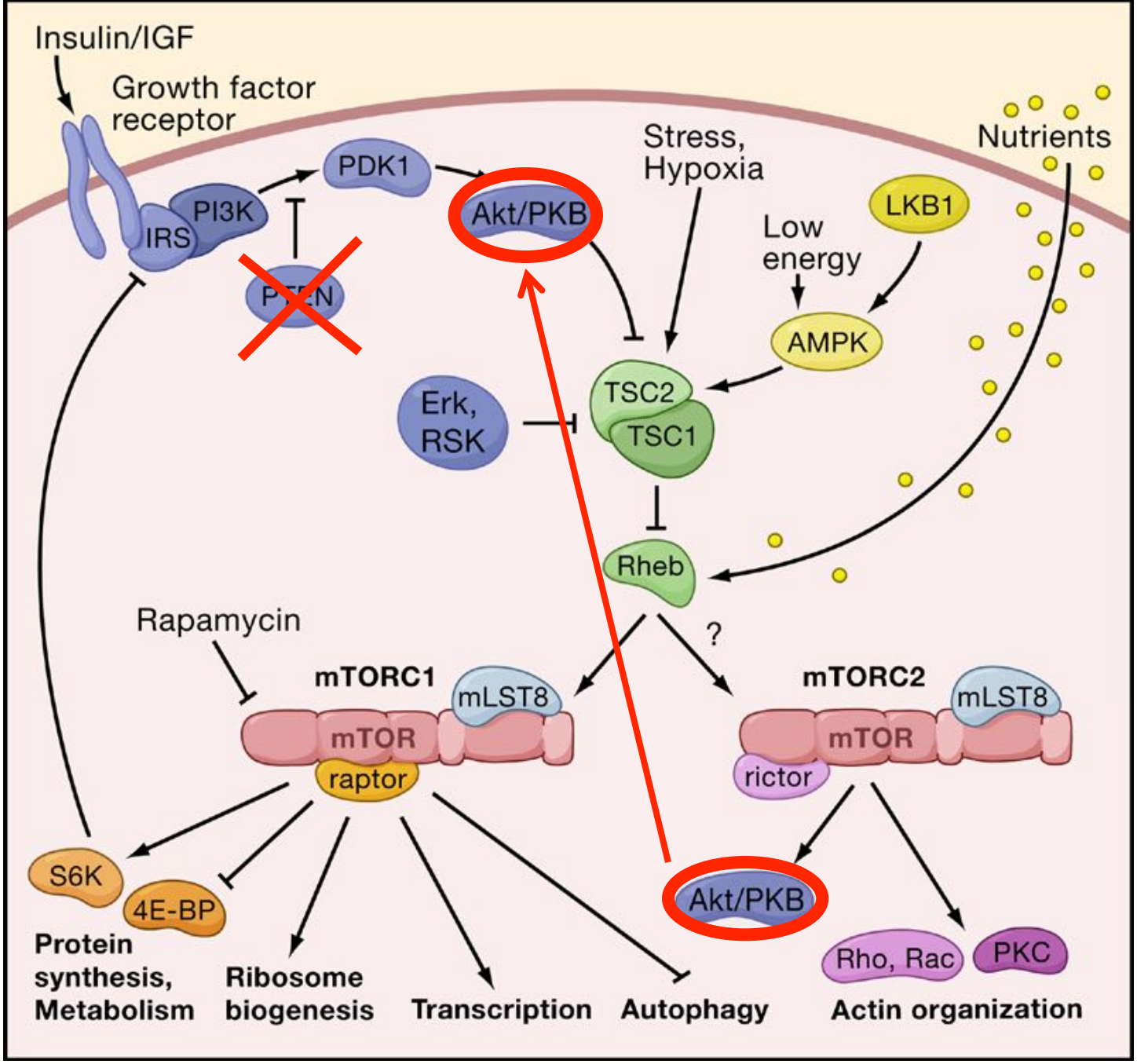

Insulin or
IGF-1 receptor
IRS-1
PIP2
PIP3
PTEN
PI-103
p85
Ras
p110α
PI3K
PI-103
PKA
PKC
PDK1
Thr308
p70S6K
PKB/Akt
Ser473
mTOR
Rictor
GβL
Raf
MEK
ERK
PI-103
IRS-1
TSC1
TSC2
PI-103
Cyclin D1
GSK-3
Forkhead
BAD
mTOR
Raptor
GβL
Cell cycle
progression
and
proliferation
p27
FasL
Bcl-2
Glucose
metabolism
Survival
Protein synthesis
and cell growth
Bob Crimi

mammalian TOR complexes

tuberous sclerosis proteins:
TSC1 (hamartin)
TSC2 (tuberin).

mTorc1 and mTorc2=mTorCOMPLEX

Rheb = (Ras homolog enriched in brain) GTP-binding protein



Stephan Wullschleger,1,3 Robbie Loewith,2,3 and Michael N. Hall1, "TOR Signaling in Growth and Metabolism
Cell *124*, February 10, 2006

Pharmacogenomics in Action

The Intricacies of Applying Genotyping to the Treatment of Patients

- Two ways in optimizing the ultimate efficacy and minimizing the toxicity of a therapeutic strategy:
  - antineoplastic agents specifically and prospectively targeted to molecular abnormalities within the cancers of individual Patients.
  - genetically defined features within the individual Patient's normal, rather than tumor, molecular environment.

Maurie Markman, The International Journal of Targeted Therapies in Cancer, 2012

The Path Ahead
Eight Suggestions for the Next 15 Years

- *Smarter target selection* –more cancer specific
- *Better drugs; more robust preclinical data*
  - How much inhibition is enough? Is it achievable
  - Anticipate resistance
  - Consider alternative schedules of administration
- *Adequate proof of concept in humans*
  - *Enough* inhibition at safe doses to warrant development
- *Invest in clinical biomarker development – early*

The Path Ahead
Eight Suggestions for the Next 15 Years

- *Set higher bar for efficacy* in early clinical trials using meaningful clinical endpoints
- *Don't completely forget about cytotoxic chemotherapy*
- *Find the right balance between speed and perfection*

The Path Ahead
Eight Suggestions for the Next 15 Years

- *Set higher bar for efficacy* in early clinical trials using meaningful clinical endpoints
- *Don't completely forget about cytotoxic chemotherapy*
- *Find the right balance between speed and perfection*
- *Stay optimistic*
  - *We have promises to keep and miles to go before we sleep…*