AVANCES EN LA GESTIÓN ASISTENCIAL FRENTE AL CÁNCER
BARCELONA, 4 de Julio de 2011

FUNDACION BAMBERG

Avances en el diagnóstico y terapia del cáncer. Nuevos fármacos en Oncología

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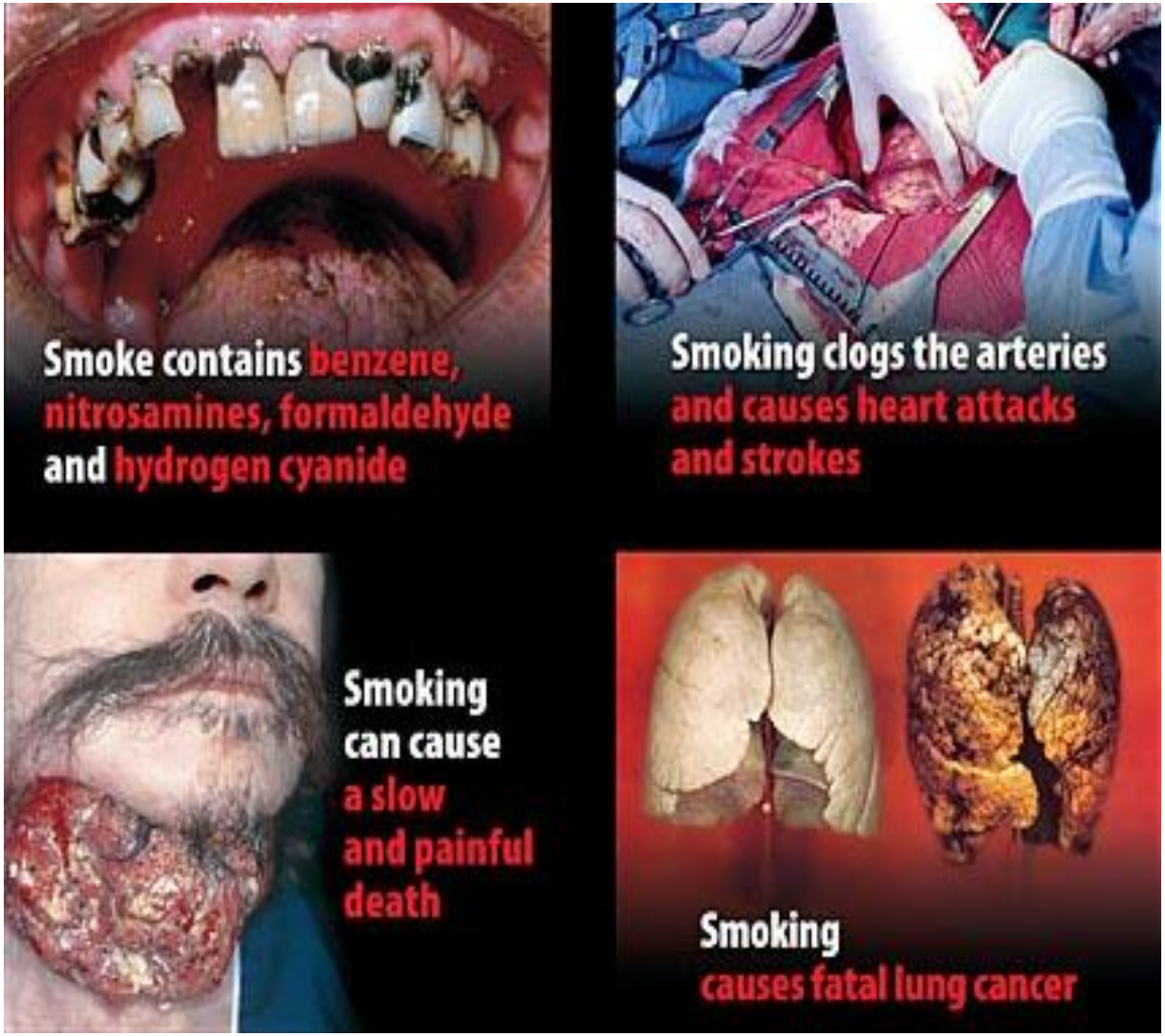
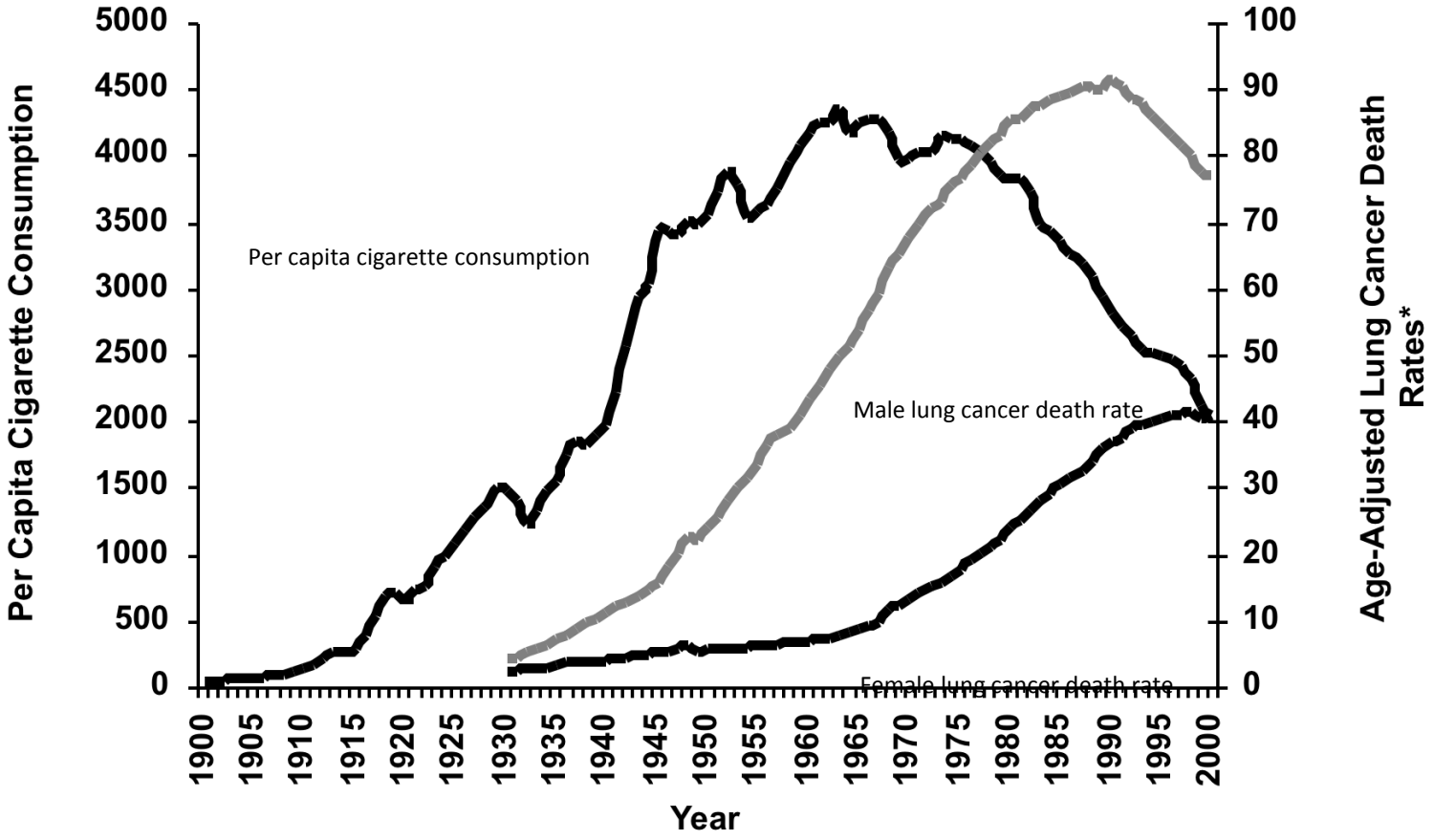
FRENTES EN LA LUCHA CONTRA EL CÁNCER

- Prevención primaria (Hábitos saludables, vacunas, fármacos, cirugía, etc.)
- Prevención Secundaria (Diagnóstico precoz o screening)
- Mejorando el diagnóstico (Tecnología)
- Aumento de conocimientos sobre la biología del cáncer (Incremento de la investigación básica, traslacional y clínica)
- Mejorando el tratamiento (Trabajo asistencial multidisciplinar, Atención integral del paciente, Investigación traslacional y clínica. Tratamientos individualizados, administrados por profesionales bien entrenados)


Smoke contains benzene, nitrosamines, formaldehyde and hydrogen cyanide
Smoking clogs the arteries and causes heart attacks and strokes
Smoking can cause a slow and painful death
Smoking causes fatal lung cancer

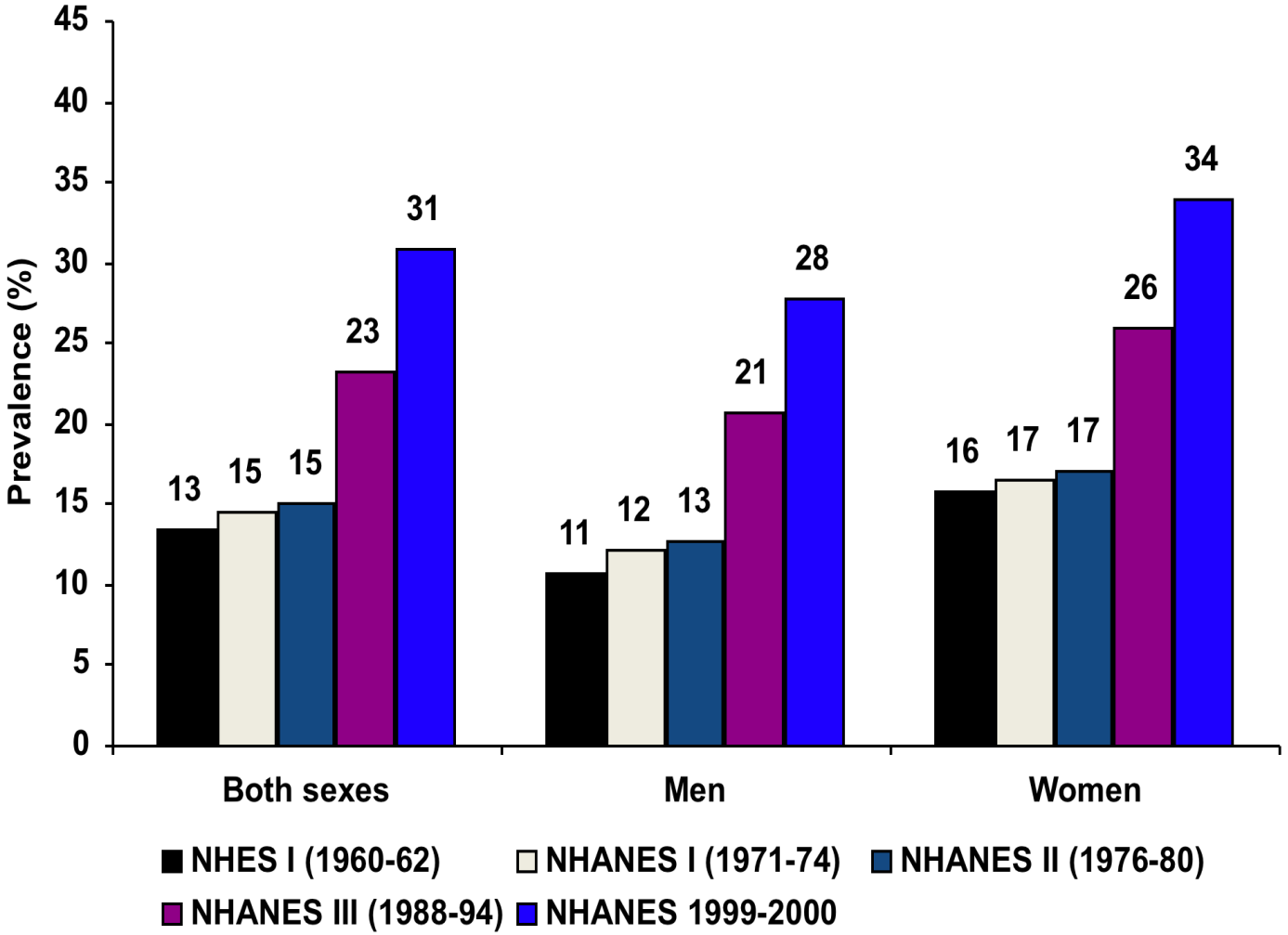
Prevention: Tobacco Use in the US, 1900-2000



***Age-adjusted to 2000 US standard population. Source: Death rates: US Mortality Public Use Tapes, 1960-2000, US Mortality Volumes, 1930-1959, National Center for Health Statistics, Centers for Disease Control and Prevention, 2002. Cigarette consumption: US Department of Agriculture, 1900-2000.**

Evitar el sobrepeso y la obesidad

Prevention: Trends in Obesity* Prevalence (%), By Gender, Adults Aged 20 to 74, US, 1960-2000



*Obesity is defined as a body mass index of 30 kg/m^2 or greater. Source: National Health Examination Survey 1960-1962, National Health and Nutrition Examination Survey, 1971-1974, 1976-1980, 1988-1994, 1999-2000, National Center for Health Statistics, Centers for Disease Control and Prevention, 2002.

Hacer ejercicio físico

ESTRATEGIAS DE PREVENCIÓN DEL CÁNCER

- Prevención primaria:

  Otras iniciativas

  – Vacunas (hepatitis B, HPV), fármacos, cirugía, consejo genético.
- Prevención secundaria:
  – Cáncer de mama: Mamografías anuales a partir de los 50 años
  – Cáncer de cuello uterino: Citología anual antes de los 21 años o 3 años después de las primeras relaciones sexuales vaginales.
  – Cáncer de colon y recto: Test sangre oculta en heces inmunohistoquímico anual, colonoscopia si positivo o cada 5 años
  – Cáncer de próstata: PSA y tacto rectal anual a partir de 50 años.
  – Cáncer de útero: Informar a menopáusicas riesgo de sangrado vaginal

FRENTES EN LA LUCHA CONTRA EL CÁNCER

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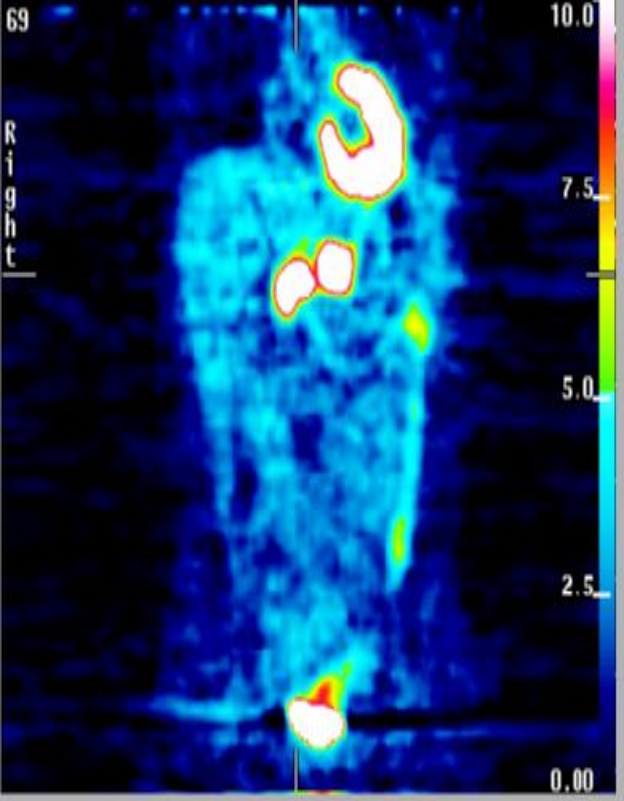
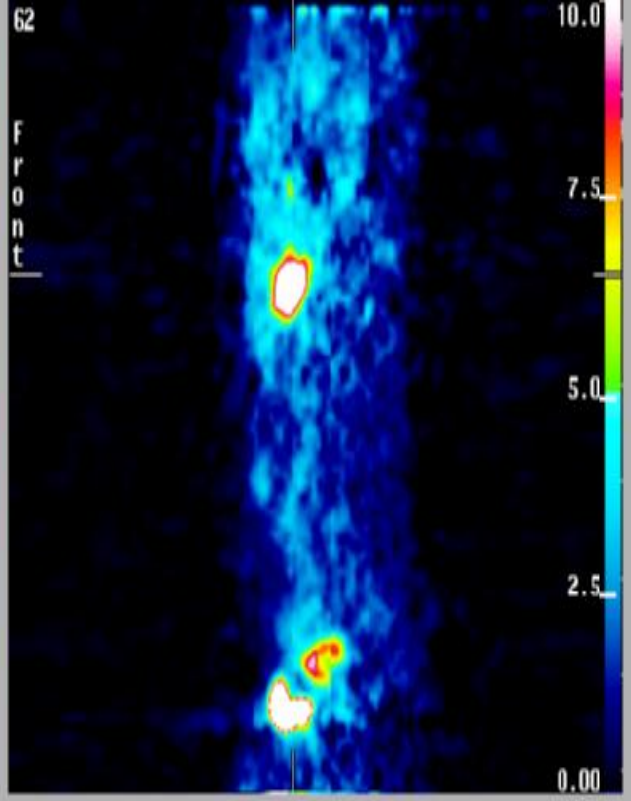
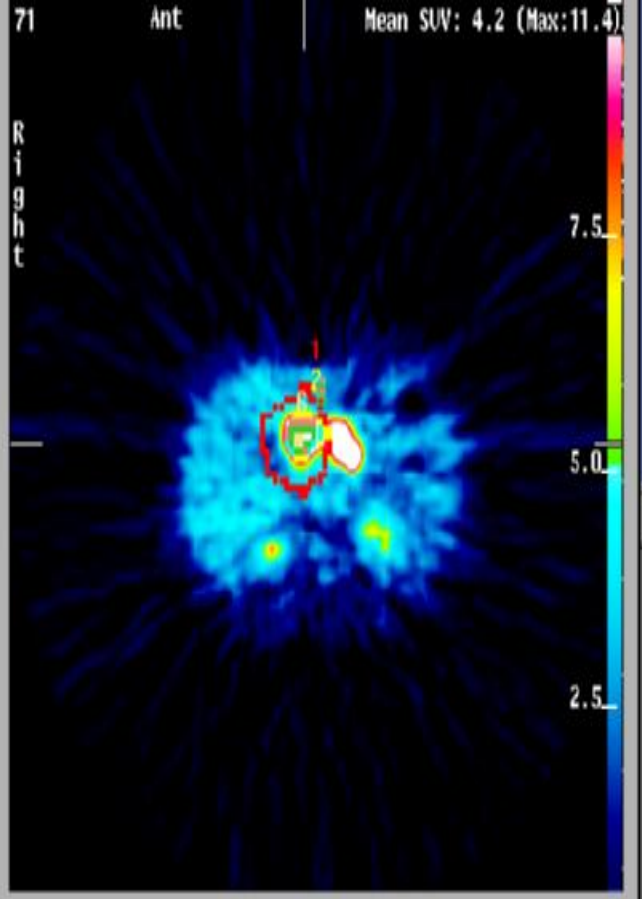
PET - TAC

- To get a good preoperative staging by detecting potentially unsuspected disease far away from the primary tumor in patients with potentially resectable metastasis.
- The reduction of tumor glucose use (FDG) after 2-4 weeks of chemo- or radiotherapy as assessed by PET imaging is correlated with tumor regression and patient outcome
- Changes in glucose metabolic activity (↓20%) may predict response only a few days after therapy





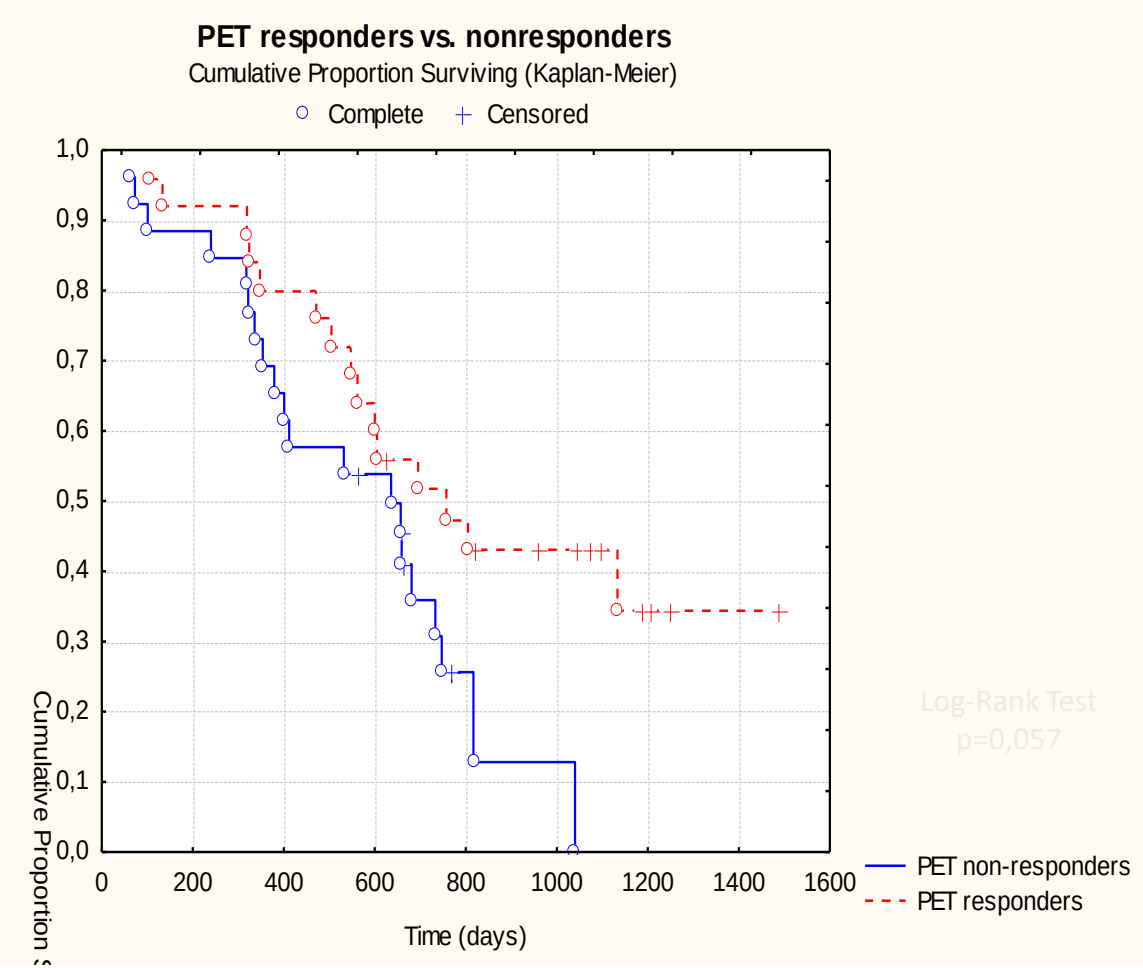


CTRL/B Toggle Marker type. Window Control Enabled. (CTRL/A to toggle)

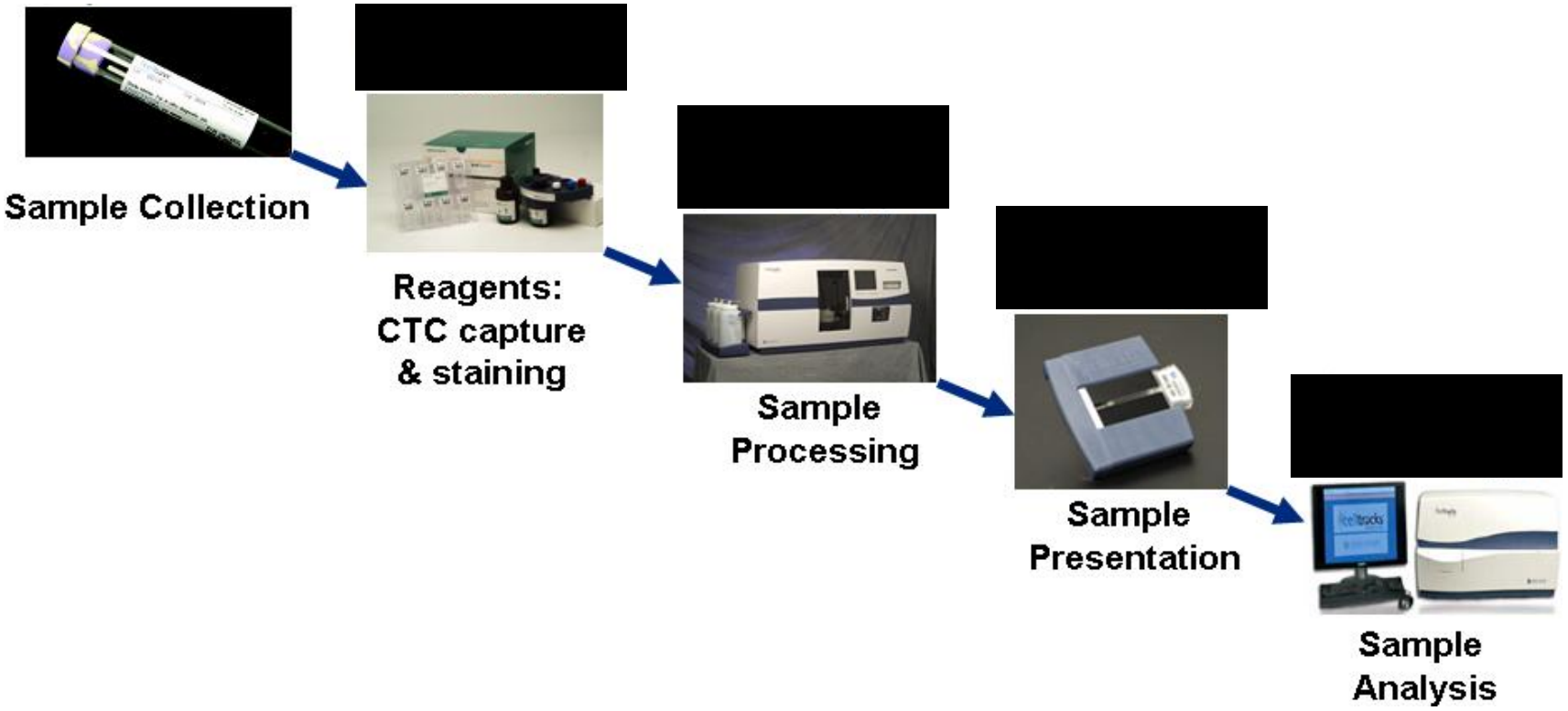
DPETS ROI Display

ROI	Cells	Total	Mean	Min	Max	Stdev	SUV Mean	SUV Max
1	170	2200380	12943	2500	34870	9100	4.2	11.4
2	47	1228470	26138	17950	34870	5163	8.6	11.4
3	34	976750	28728	21590	34870	3449	9.4	11.4
4	28	835280	29831	24810	34870	2597	9.8	11.4
5	19	594690	31299	28230	34870	1641	10.2	11.4
6	4	133780	33445	31820	34870	1183	10.9	11.4

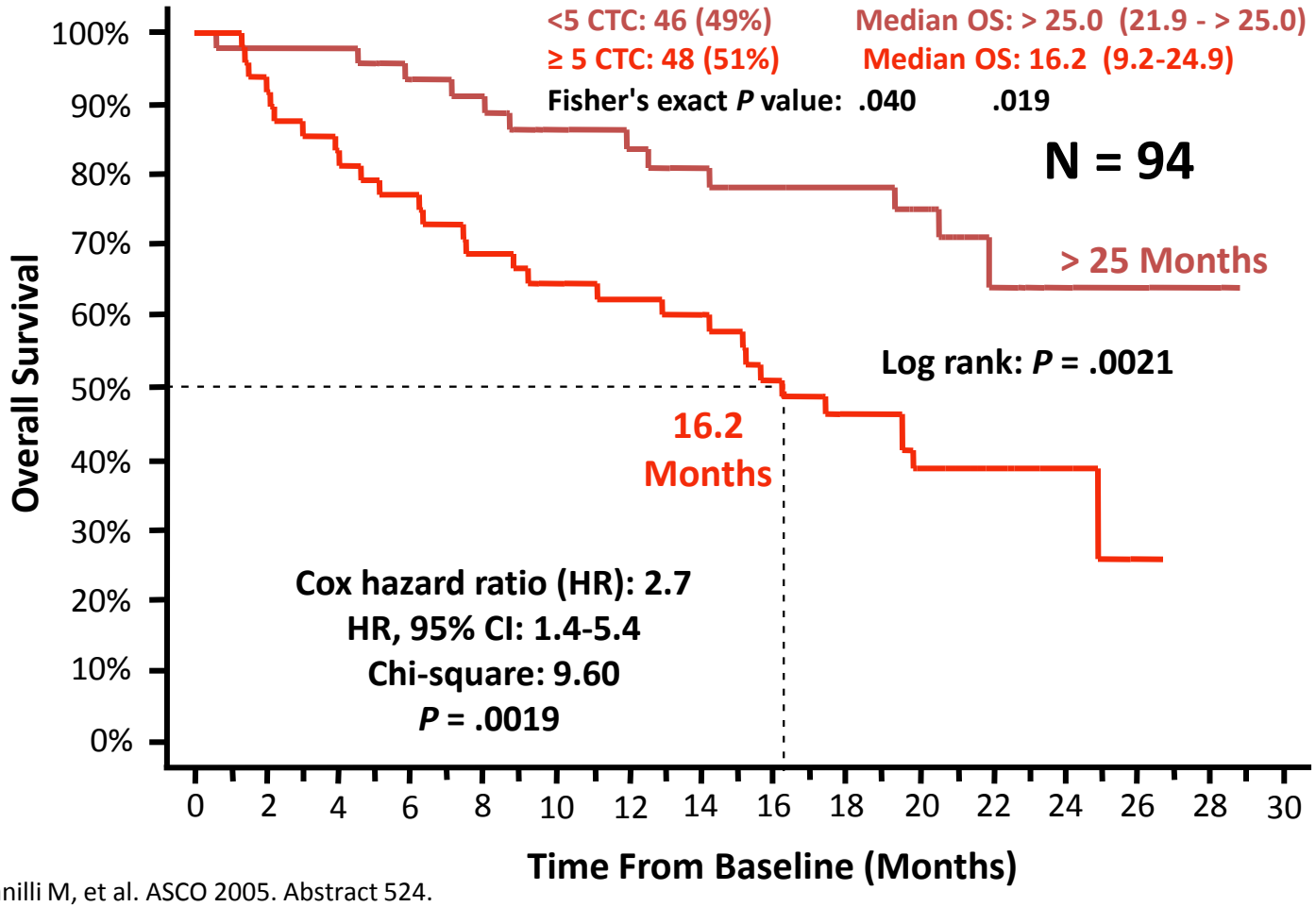
PET response and correlation with survival



CellSearch System for Circulating Tumor Cells

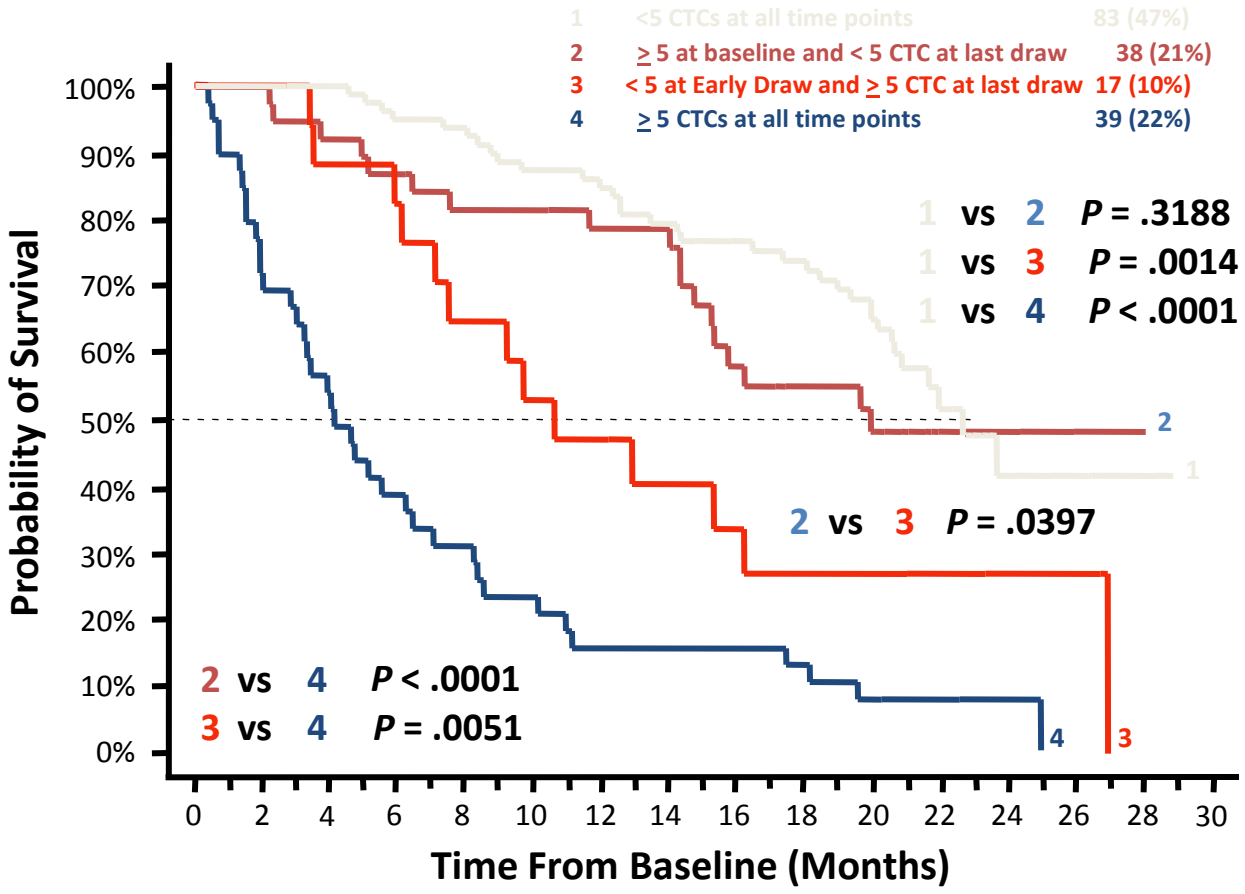


Newly Diagnosed MBC
Baseline CTC Counts Predict OS



Cristofanilli M, et al. ASCO 2005. Abstract 524.

Change in CTC Count During Therapy Predicts Overall Survival



Cristofanilli M, et al. ASCO 2005. Abstract 524.

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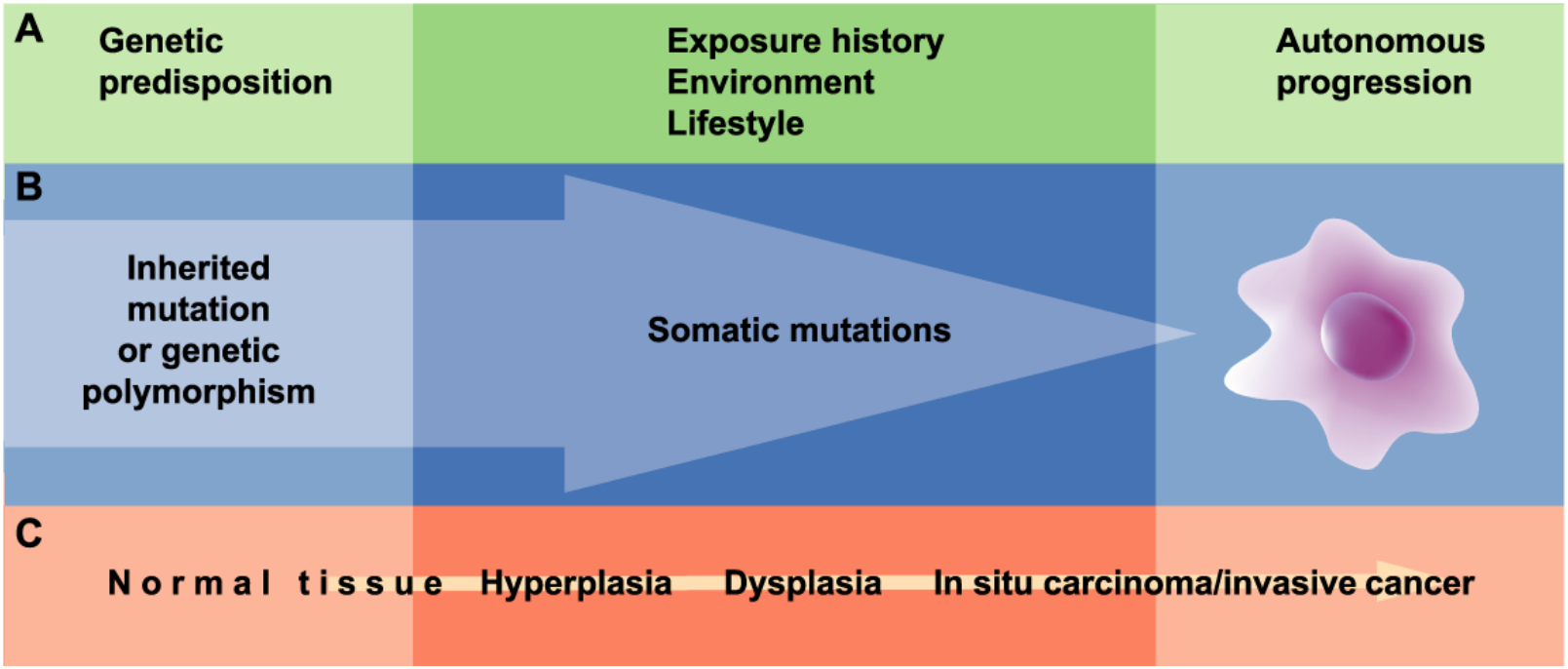
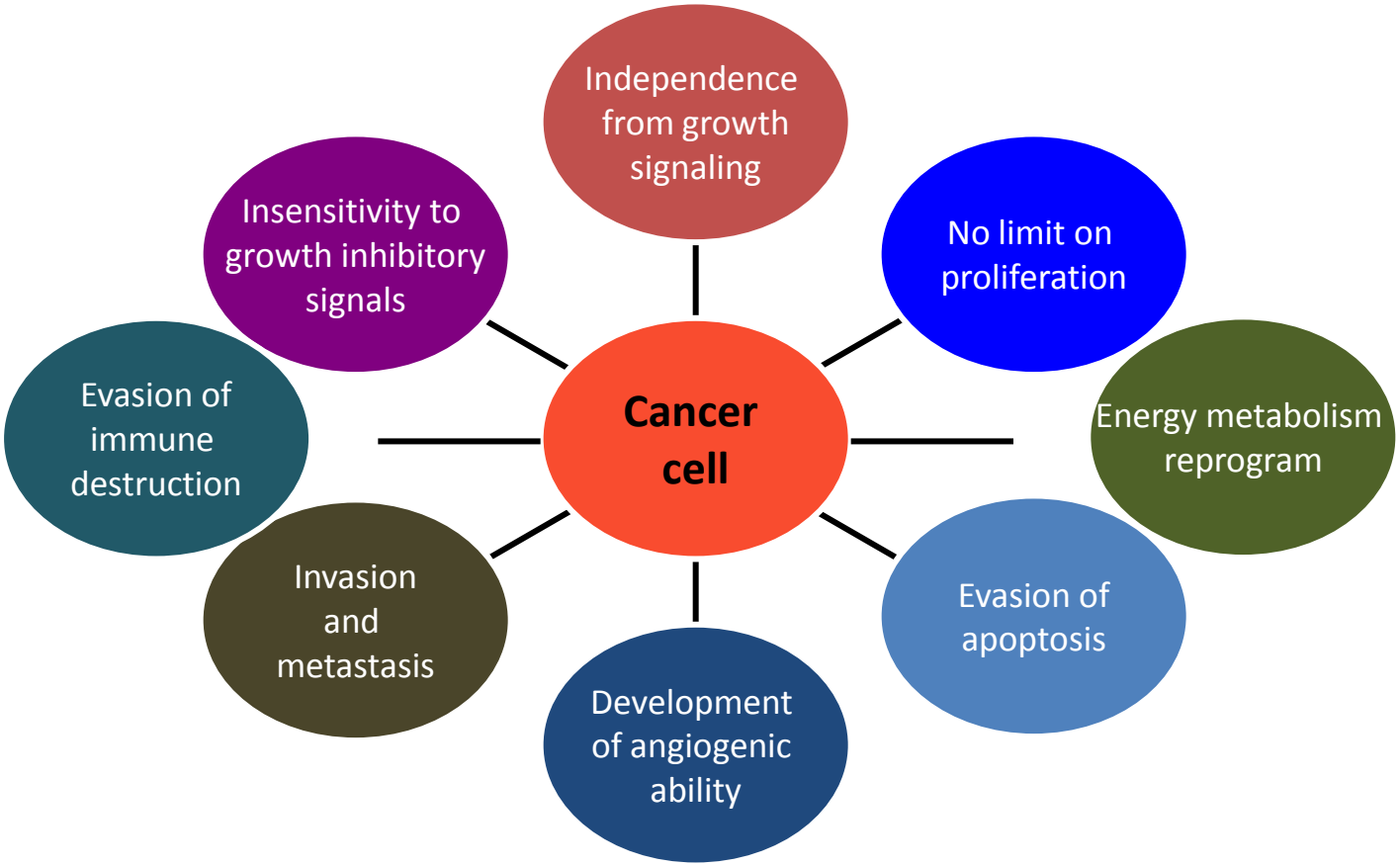
Development of Cancer



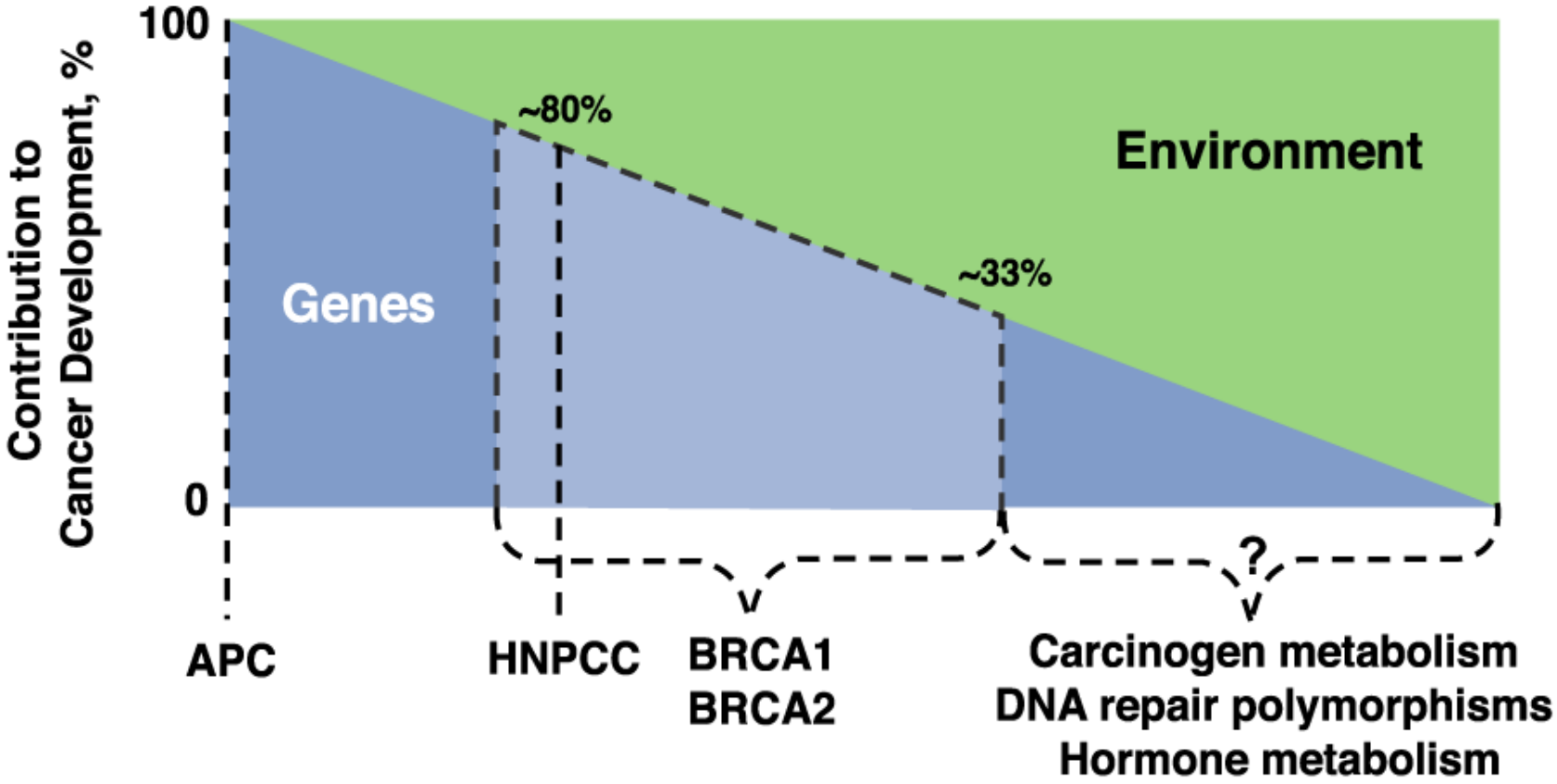
A, Factors contributing to the generation of the cancer cell. B, The effects of these factors on the cell. C, Pathologic outcome. Progression from normal tissue to invasive cancer.

Hallmarks of Malignancy



Hanahan D, et al. Cell. 2011 Mar 4;144(5):646-74.

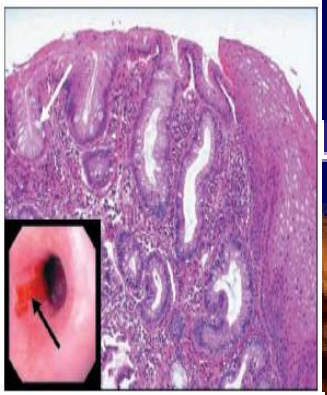
Gene-Environment Interaction and Likelihood of Developing Cancer



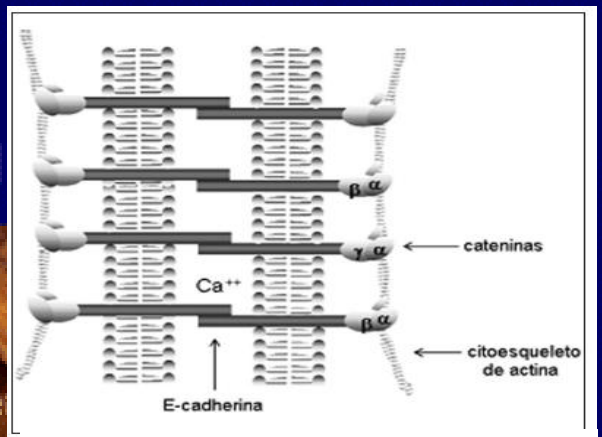
A cancer gene could be expressed without any environmental influence or only when activated by environmental factors.

Lichtenstein P. N Engl J Med 2000; 343:78-85

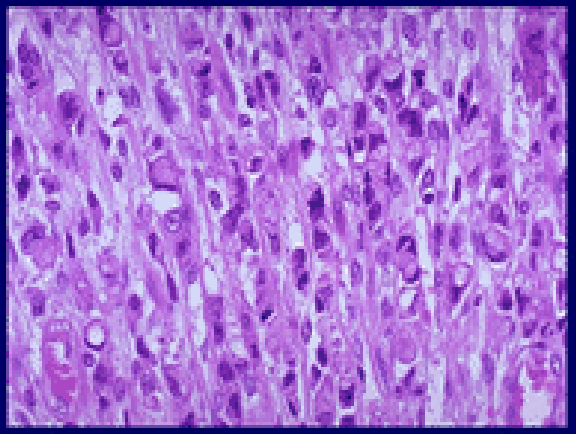
GASTRIC CANCER PATHOLOGY



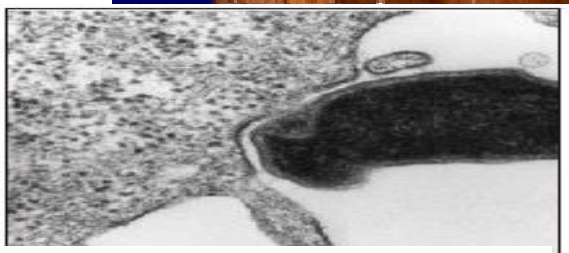
BARRET'S EPITHEL.



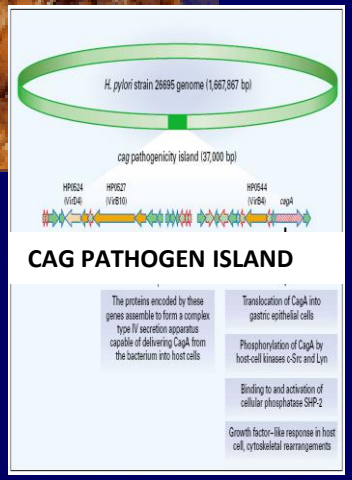
E-CADHERIN GERMLINE MUTATIONS



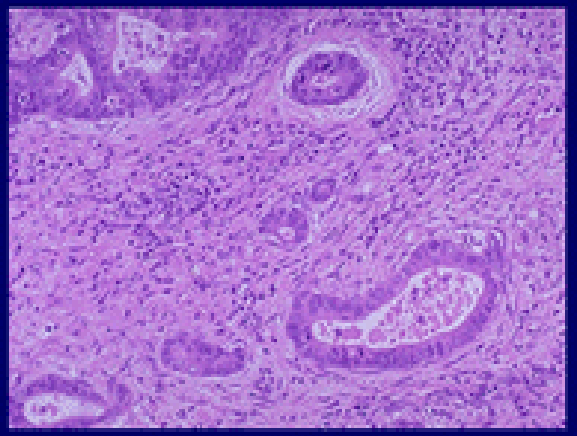
DIFFUSE TYPE



HELYCOBACTER PYLORI INFECTION

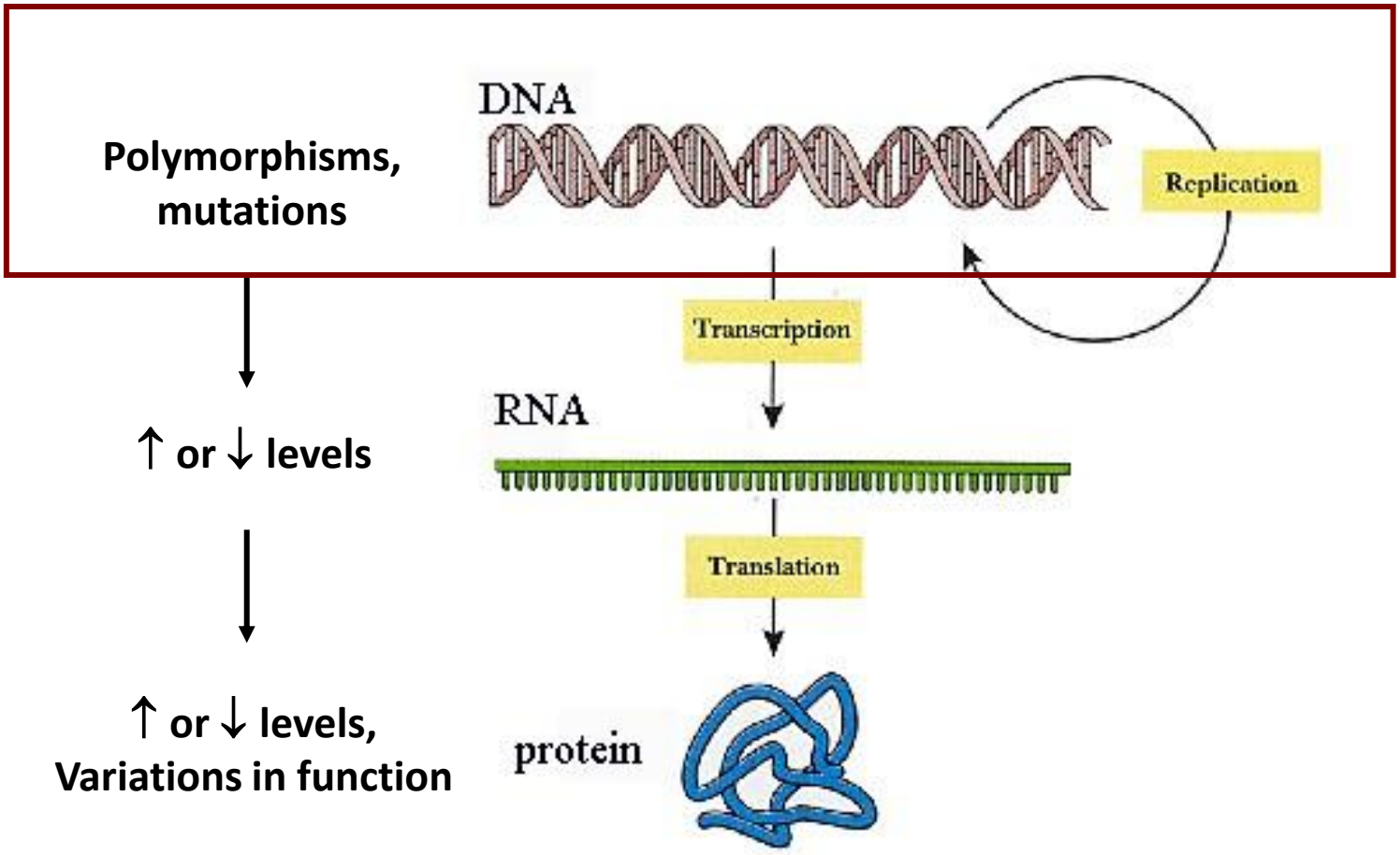


CAG PATHOGEN ISLAND



INTESTINAL TYPE

Different ways of genetic variability



ANTI CANCER DRUG ACTIVITY AND POLYMORPHISMS

PREDICTORS

DRUG

UPTAKE / EFFLUX

CONCENTRATION

METABOLIZING ENZYMES

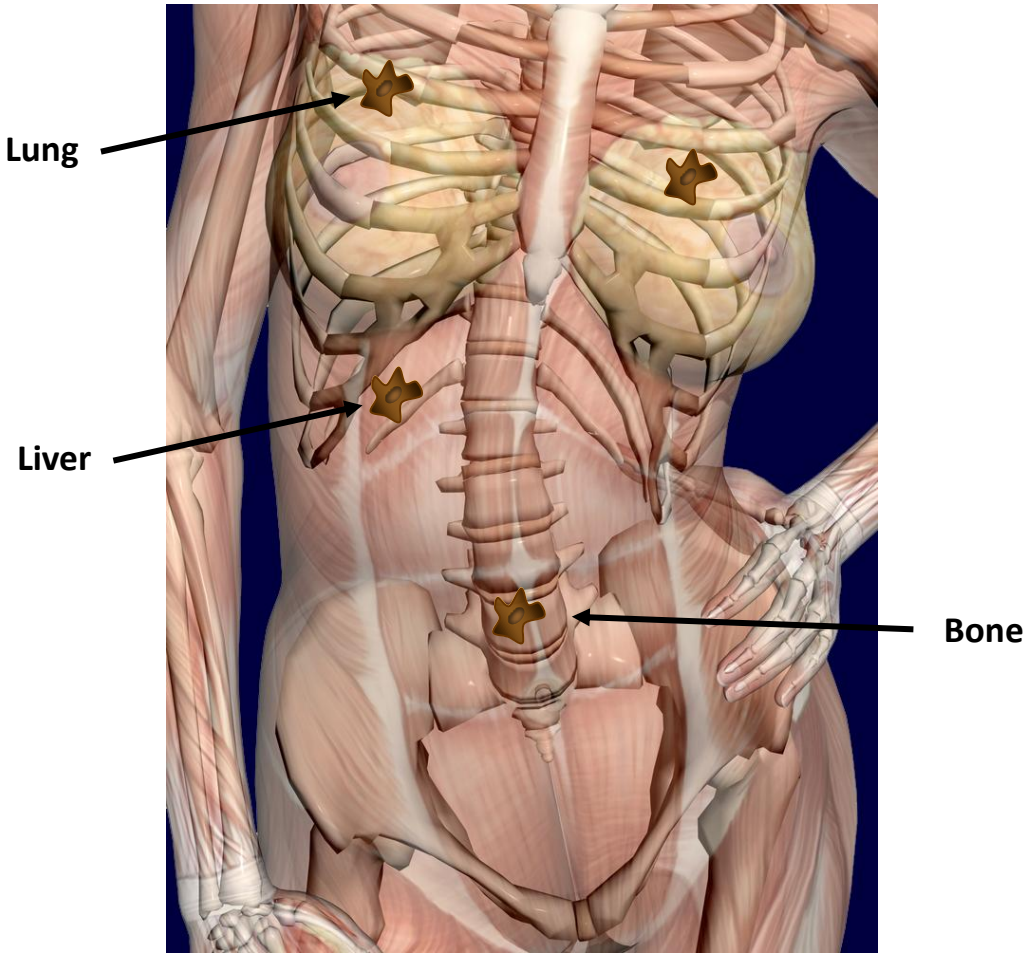
APOPTOSIS / DEATH

DNA REPAIR

TARGET

(GENE OVEREXPRESION
DOWNREGULATION
MUTATIONS)

Metastatic Process: Arrest in Host Organs



Adquisición del fenotipo invasivo y metastásico

- Cambios observados en el fenotipo de las células con capacidad de invadir y metastatizar:
  - ↓ complejo cadherina/catenina que forma parte de las uniones intercelulares
  - ↑ de la expresión de las integrinas de la membrana celular, que interaccionan con componentes de la matriz extracelular
  - ↑ de la secreción de proteasas
  - Angiogénesis

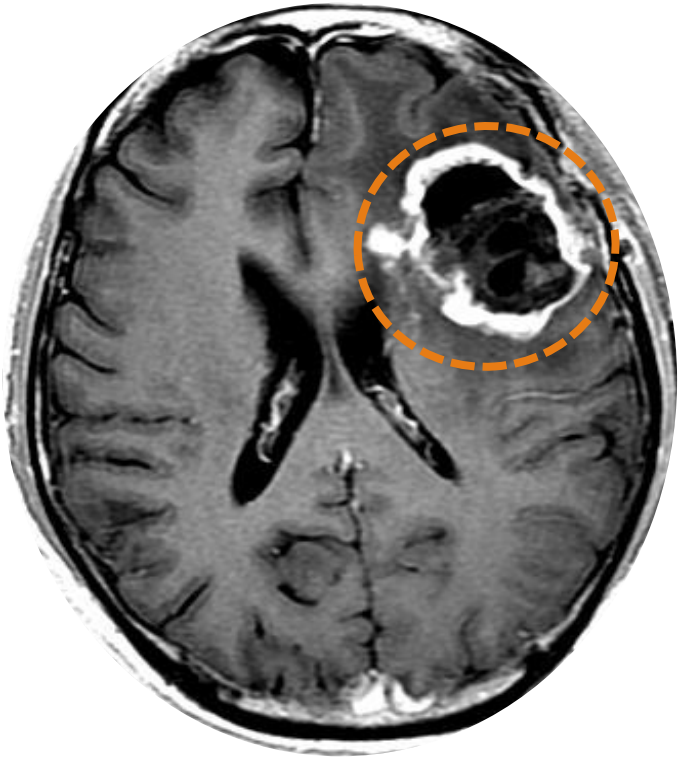
Pipeline of a Pharma Company

TUMOR CELL	Phase I	Phase II	Phase III	Submitted
Cetuximab (varying by indication)		X	X	
c-Met kinase inhibitors (EMD 1214063; EMD 1204831)	X			
MEK inhibitor (AS703026/MSC1936369B)	X			

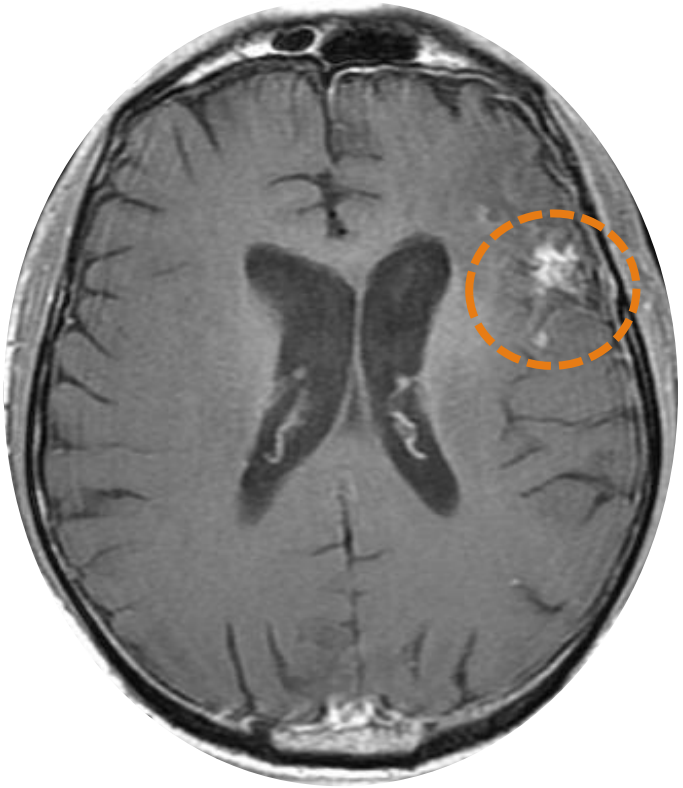
TUMOR ENVIRONMENT	Phase I	Phase II	Phase III	Submitted
Cilengitide (integrin inhibitor)		X	X	
Anti-integrin MAb (DI17E6)		X		

IMMUNE SYSTEM	Phase I	Phase II	Phase III	Submitted
MUC 1 vaccine			X	
TLR9 immunomodulator (IMO-2055)		X		

Cilengitide – PR s/a, study 009



August 2005



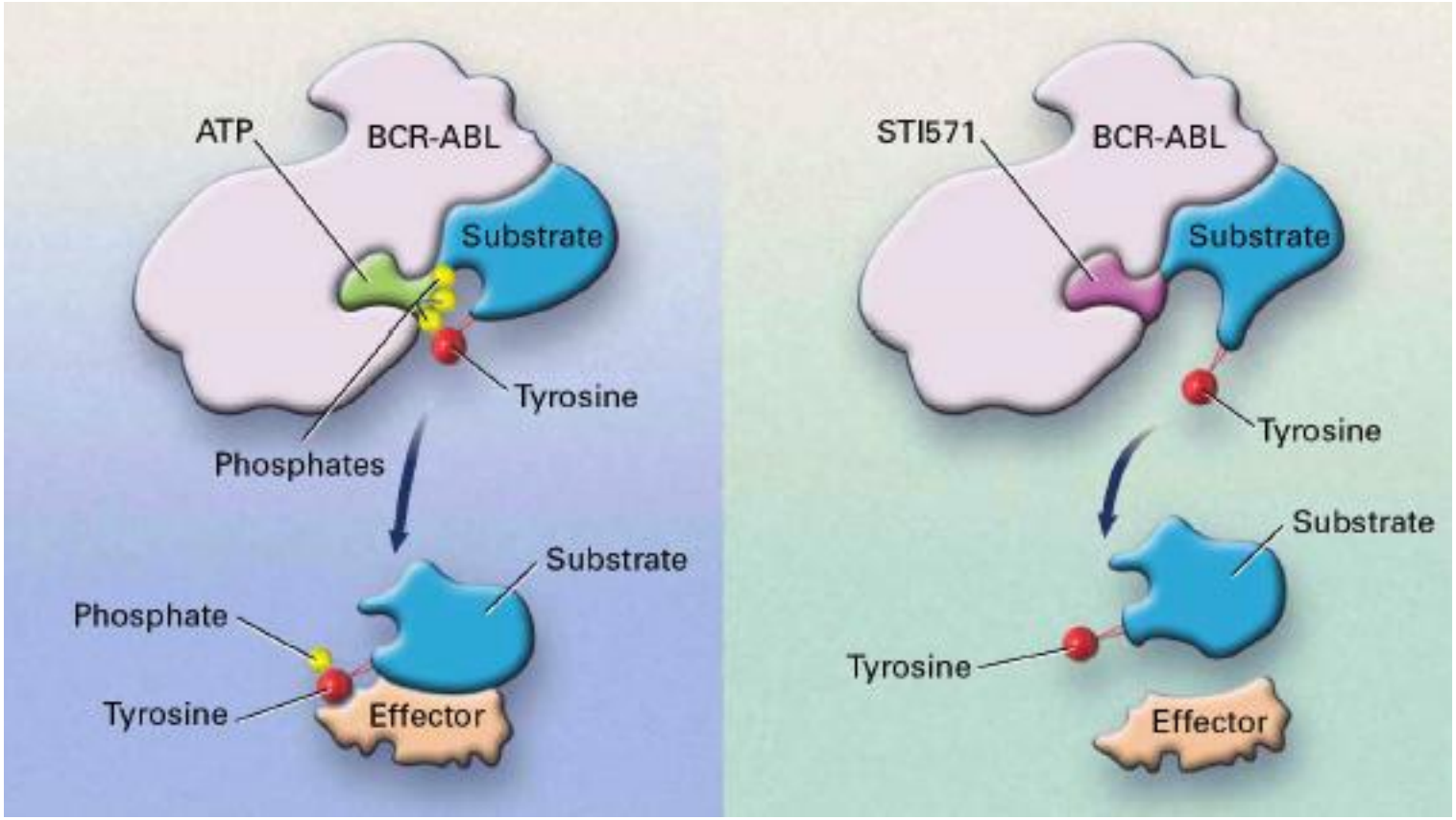
April 2006

Reardon D, et al. J Clin Oncol 2008;26:5610–17

New target-oriented drugs characteristics

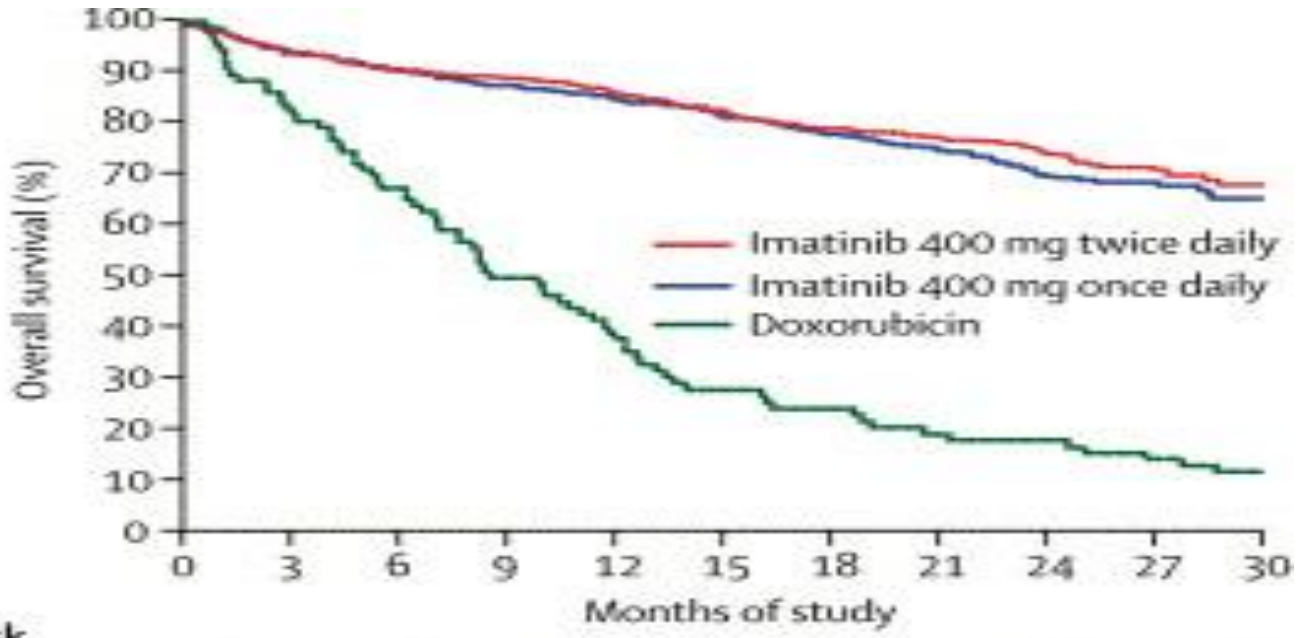
- Cell target identification
- Drug design against established targets
- More specificity
- Different toxicity to chemotherapy
- Possibility of combination with chemo- or with other target-oriented drugs
- Breast cancer endocrine therapy was the first targeted therapy

Bcr-abl in CML and c-kit in GIST



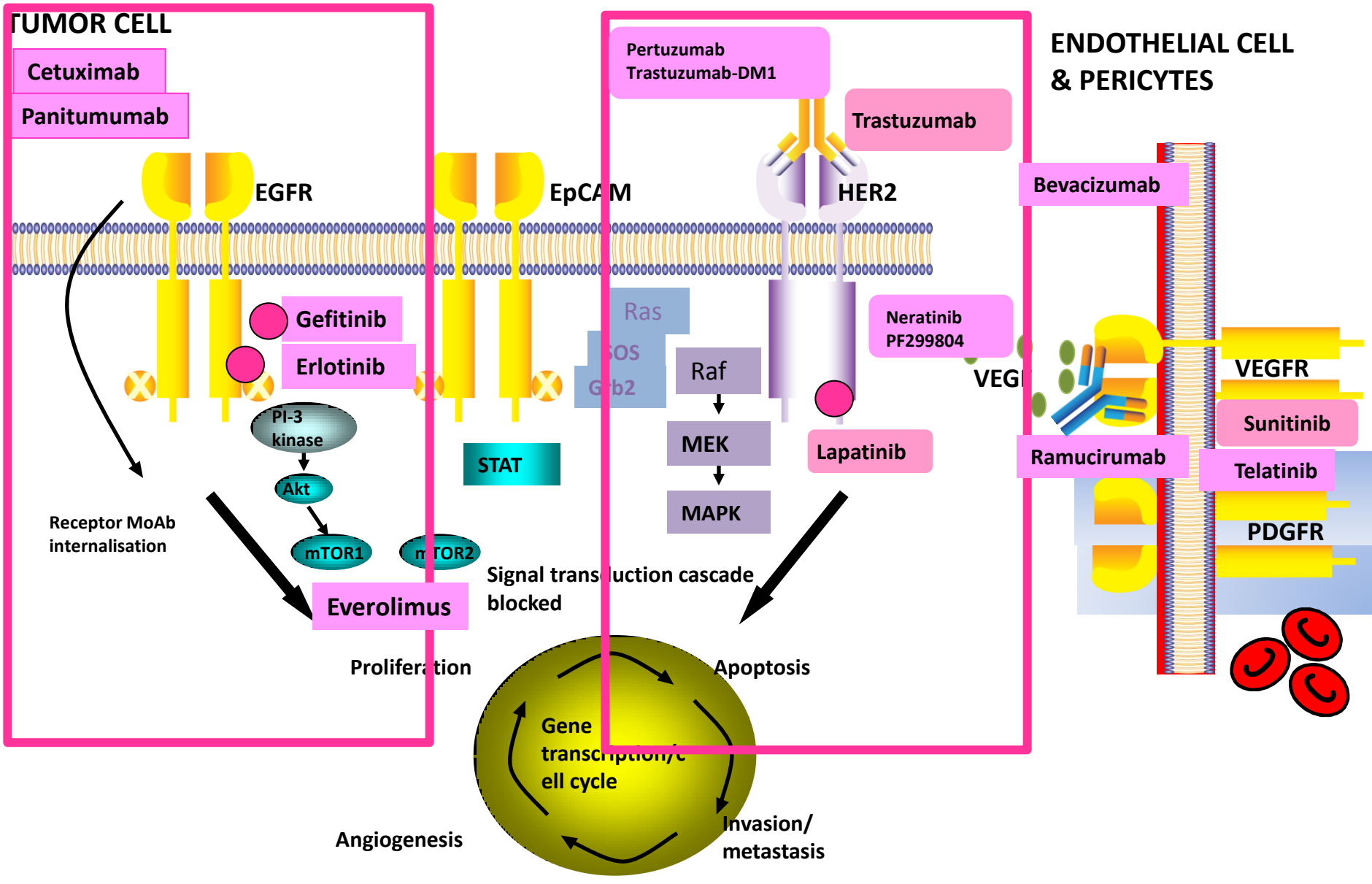
Goldman & Melo 2001

GIST: Imatinib versus chemotherapy treatment

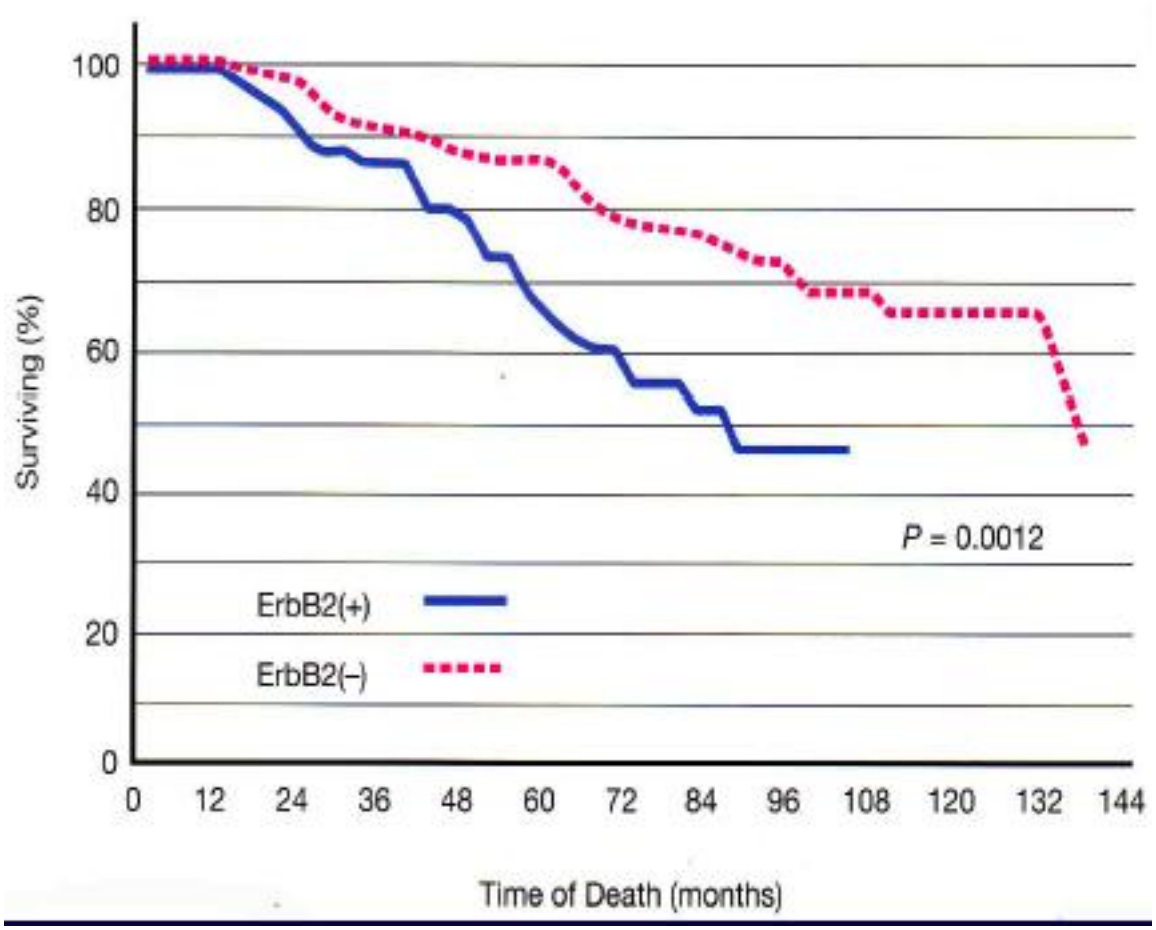


Number at risk						
Imatinib 400 mg once daily	473	423	387	315	192	49
Imatinib 400 mg twice daily	473	427	399	323	201	51
Doxorubicin	86	57	31	19	14	8

Oportunities and challenges from Molecular Basis

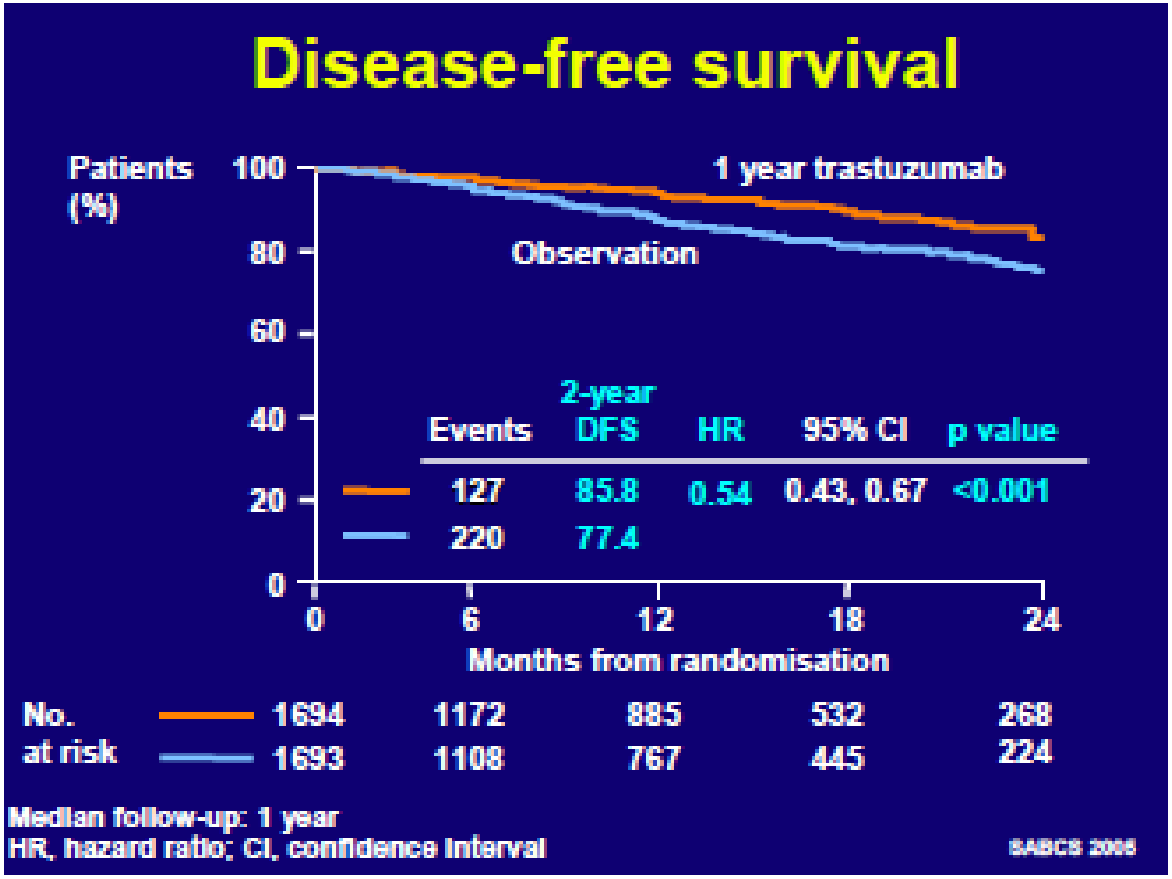


Correlation of ErbB2 expression with survival in breast cancer patients



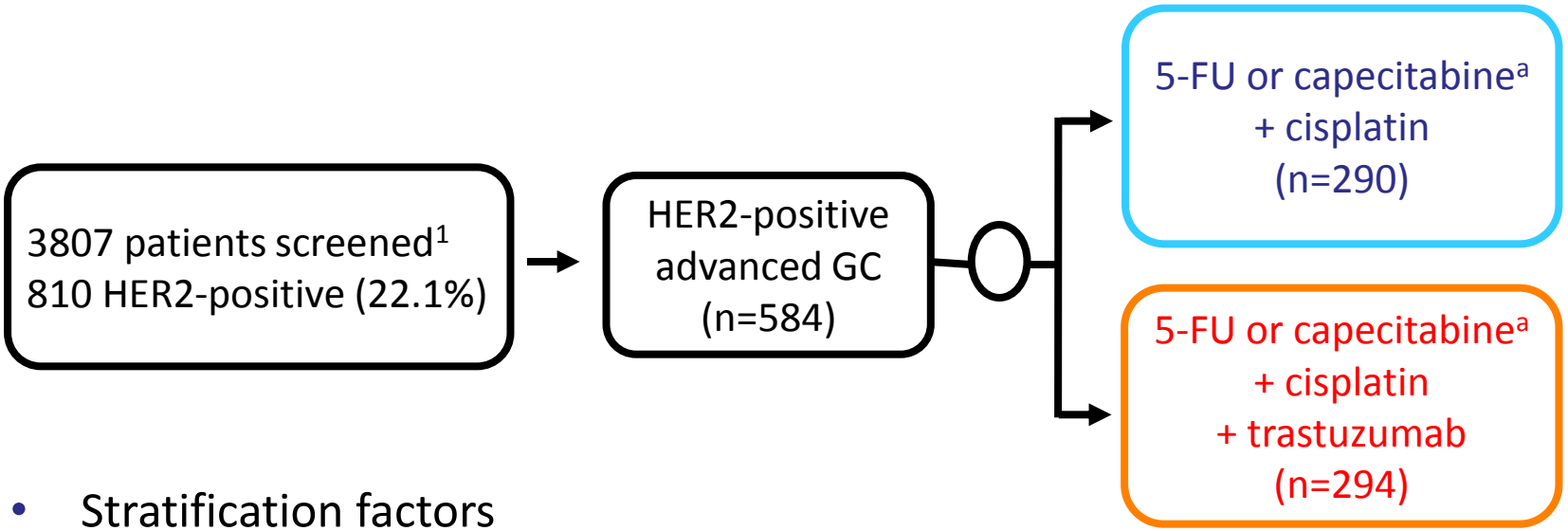
Paik J Clin Oncol 1990

HERA trial, N Engl J Med 2005



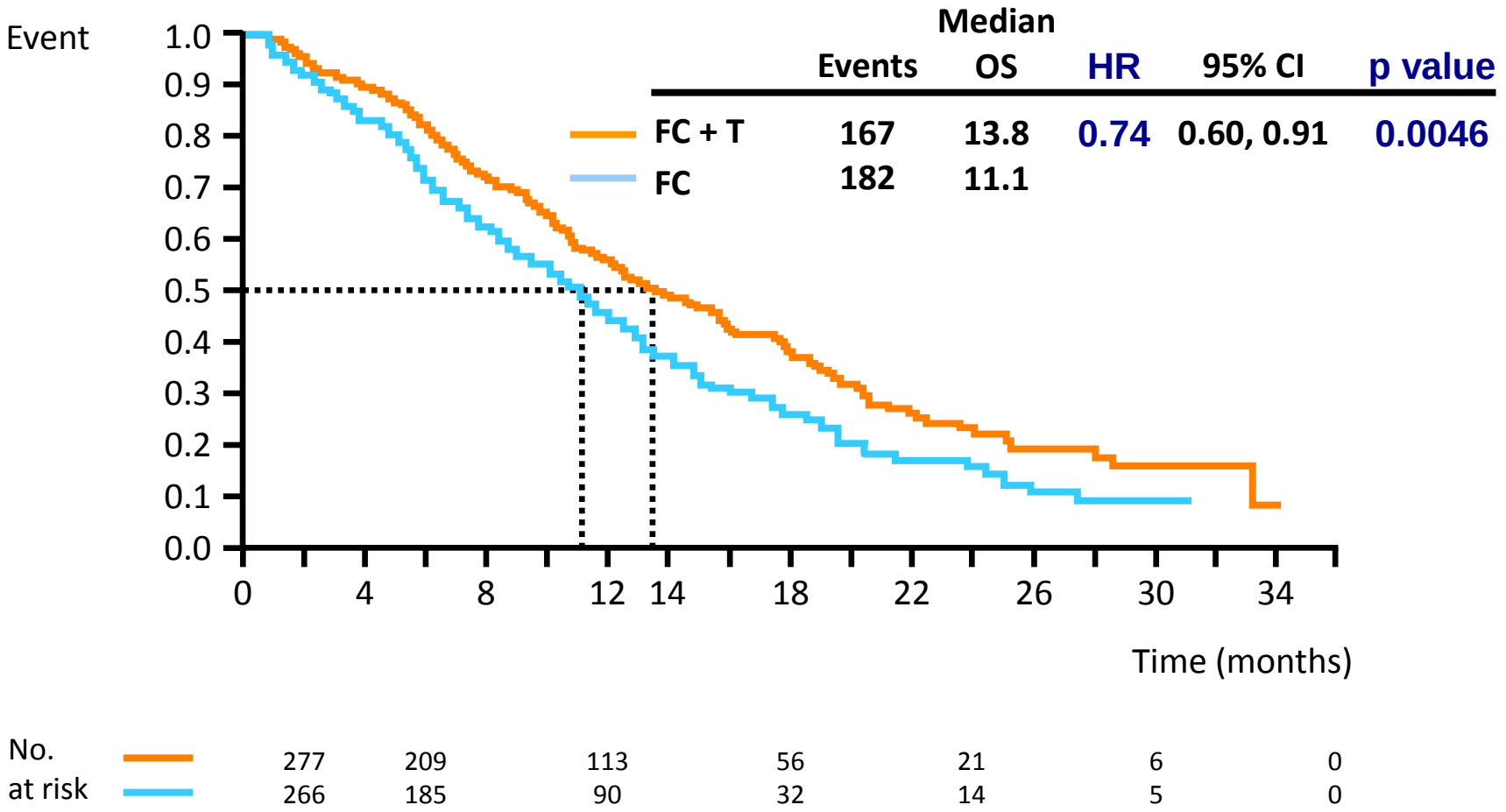
ToGA trial design

Phase III, randomized, open-label, international, multicenter study



- Stratification factors
  - advanced vs metastatic
  - GC vs GEJ
  - measurable vs non-measurable
  - ECOG PS 0-1 vs 2
  - capecitabine vs 5-FU

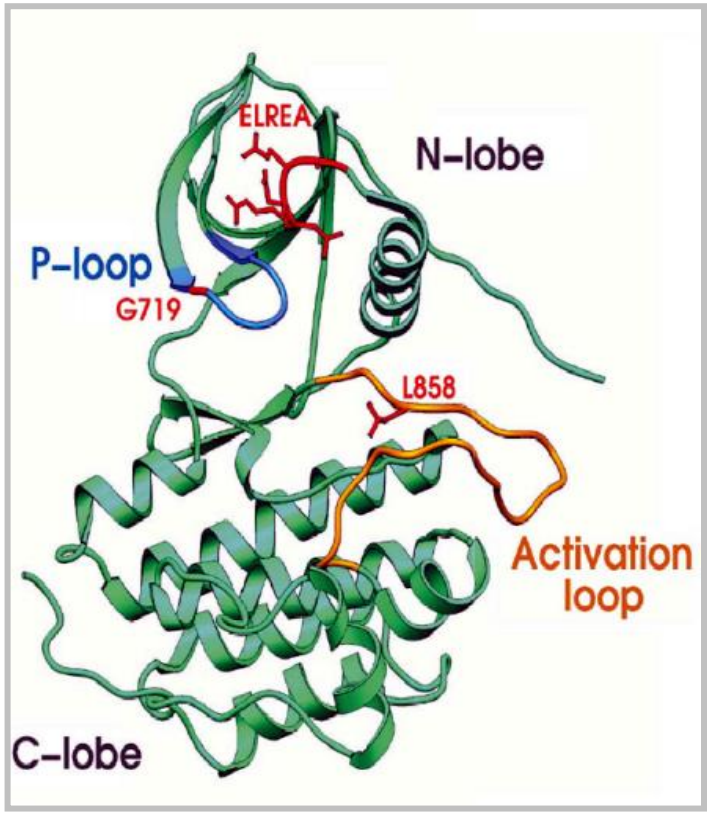
Gastric cancer OS: CF vs CF+T



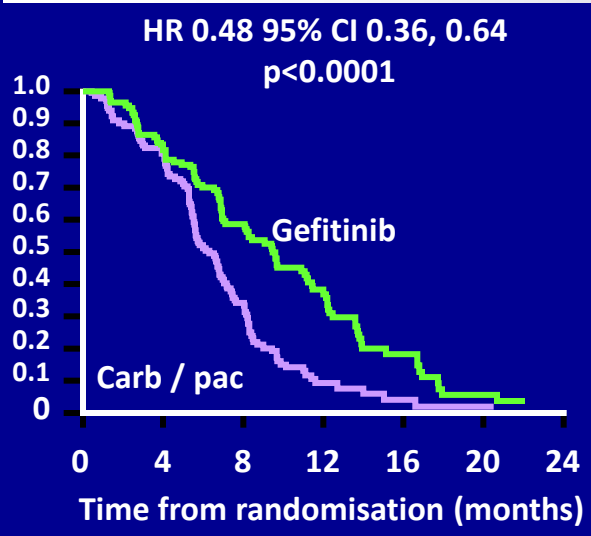
Activating mutations of the EGFR genes

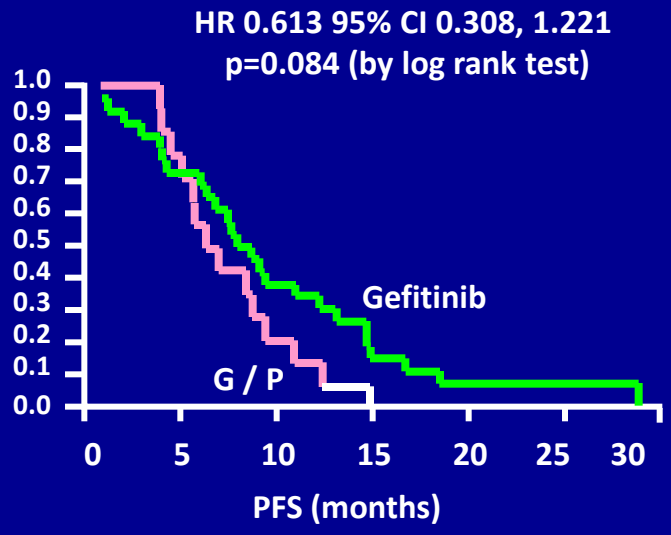
Lynch et al., NEJM, Paez et al., Science

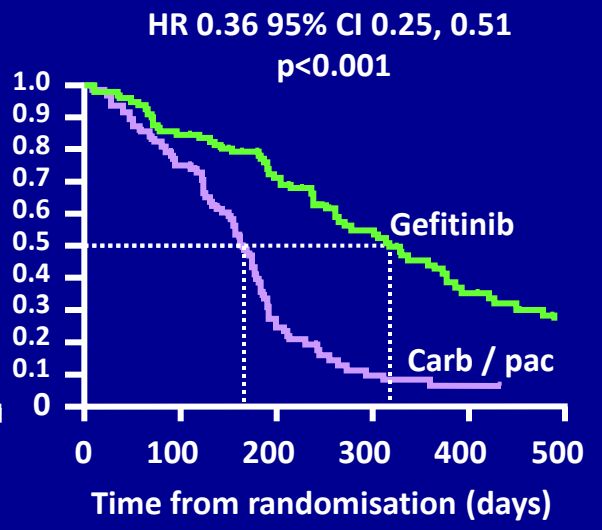
- Lung cancer specific
- In distinct subsets of patients
  - Adeno, Non smokers, Asians, Females
- Tyrosine kinase domain of the EGFR
  - Exon 19 deletion
  - L858R
  - G719, Exon 20 insertion, others
- Striking correlation with EGFR-TKI response

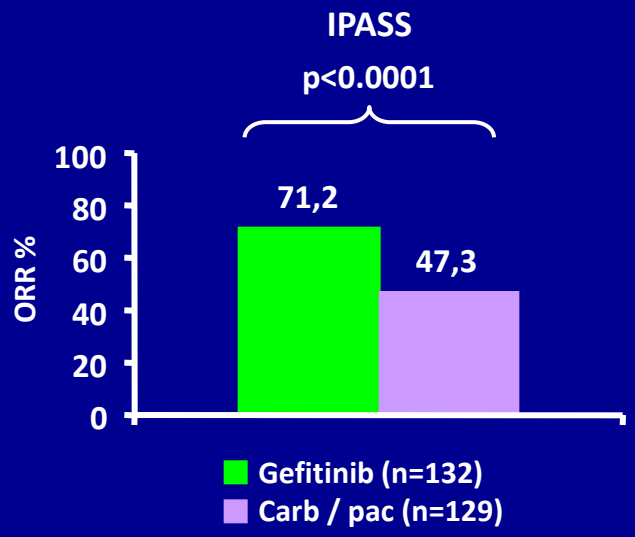


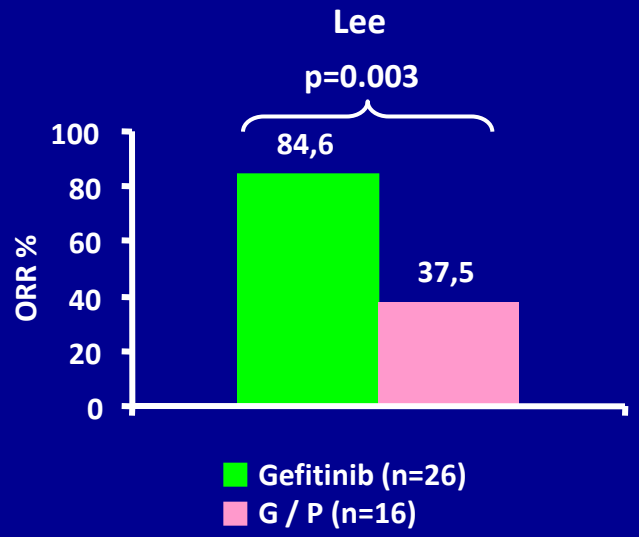
EGFR-TKIs standard of care in first-line EGFR mut+ NSCLC: Phase III study results

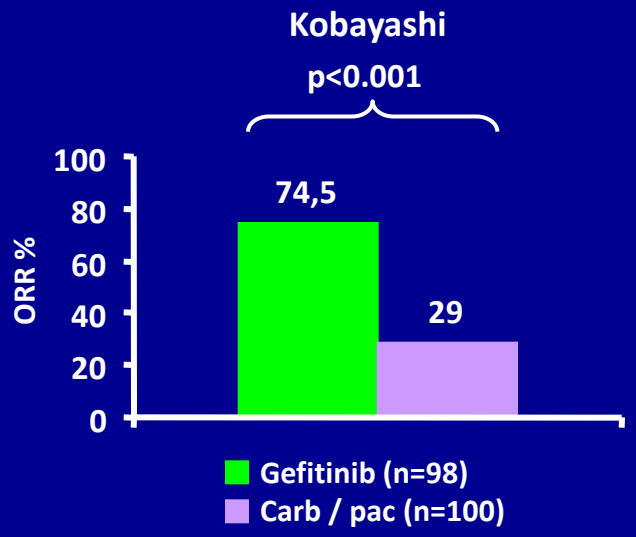












ORR, objective response rate

Mok et al 2008, Lee et al 2009, Kobayashi et al 2009

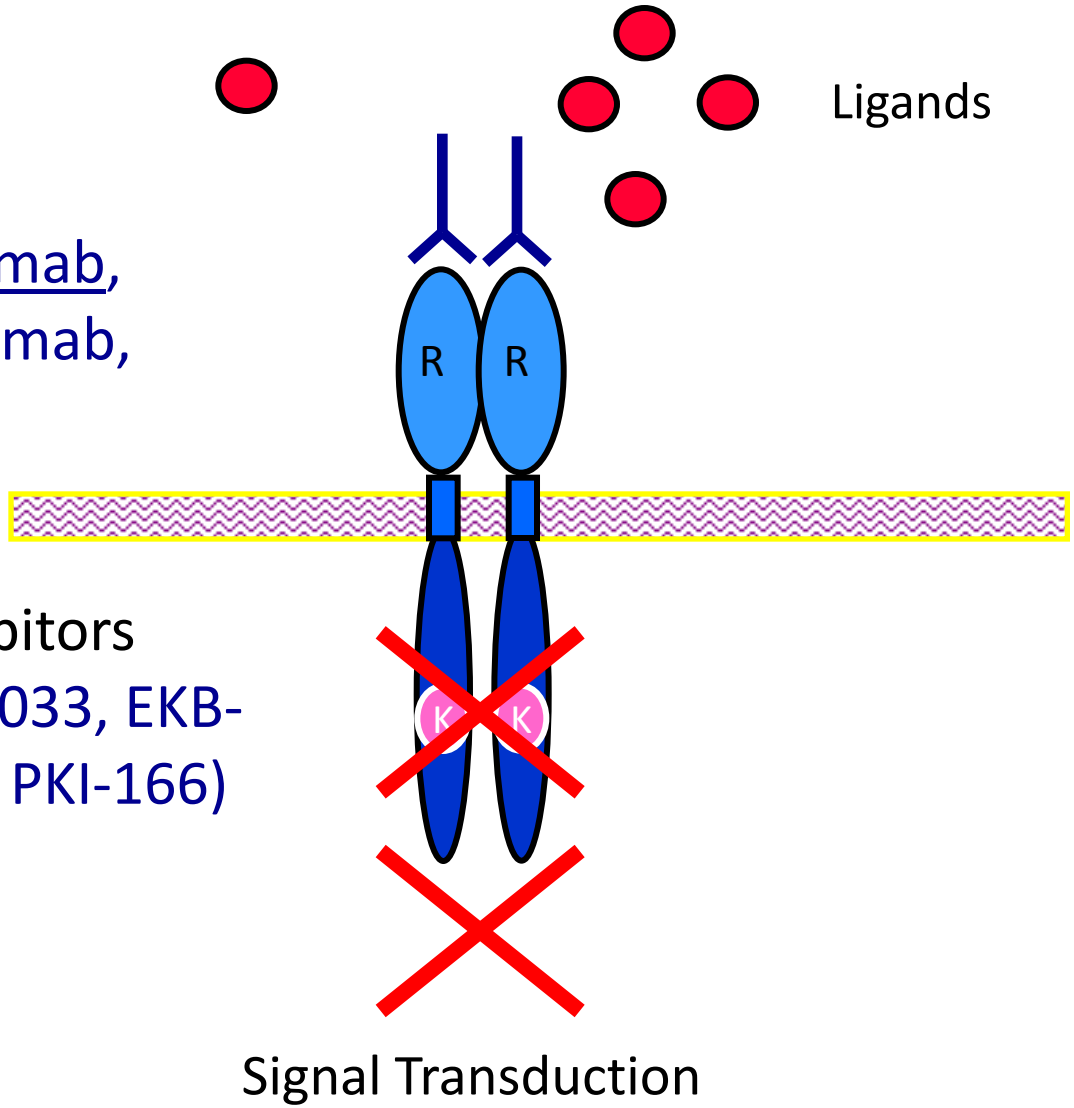
Molecular-targeted therapies

- An important molecular target for a given drug has often a significant prognostic value as it is involved in a critical function of cancer cell
- The presence of target in cancer cell is not enough to predict efficacy. Abnormalities such as gene amplification or mutation are necessary to obtain significant clinical results
- Histology and patient characteristics in some circumstances might help to select patients who will benefit from targeted therapies

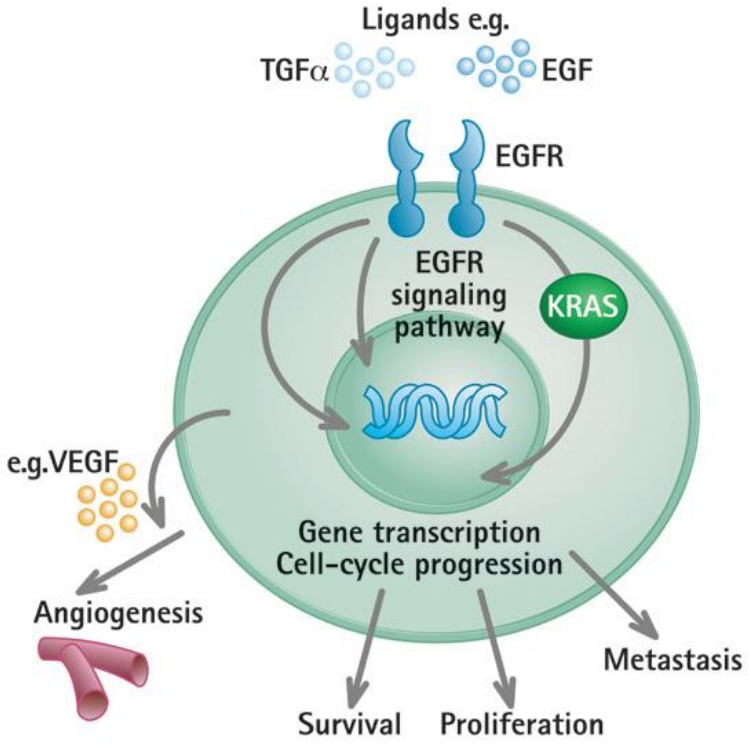
Anti-EGF Receptor Therapies

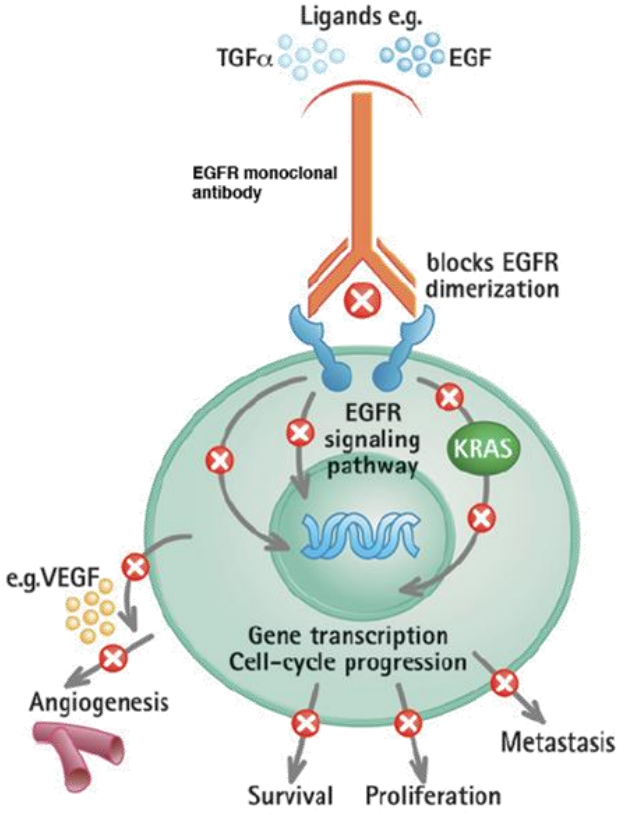
Monoclonal antibodies (Cetuximab, Panitumumab, Matuzumab, Nimotuzumab, MDX447)

Tyrosine kinase inhibitors (Gefitinib, Erlotinib, CI-1033, EKB-569, AEE788, Lapatinib, PKI-166)



KRAS and the EGFR pathway

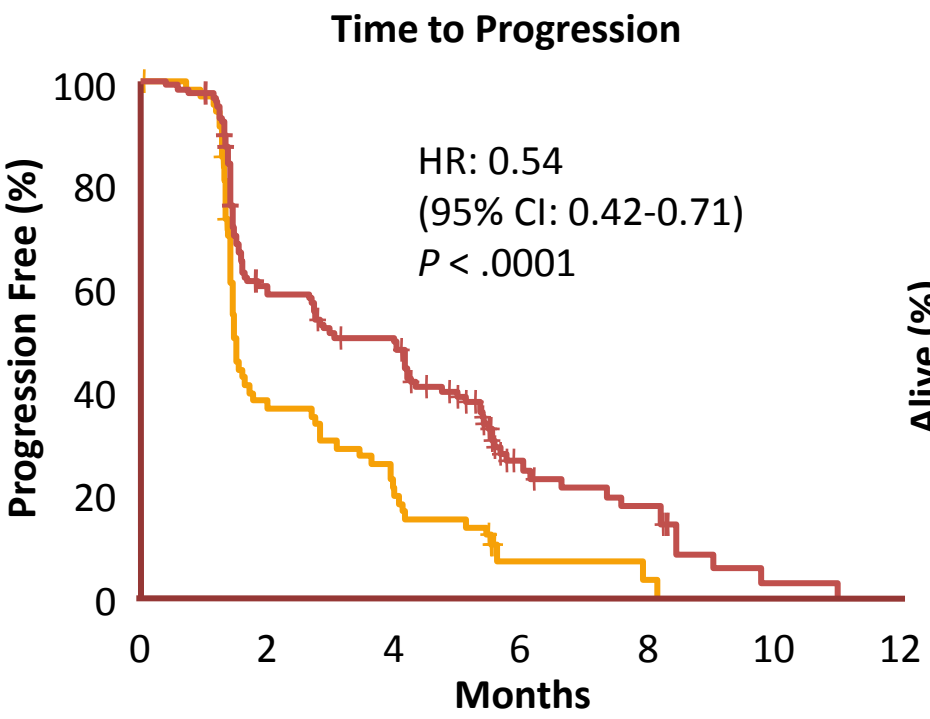


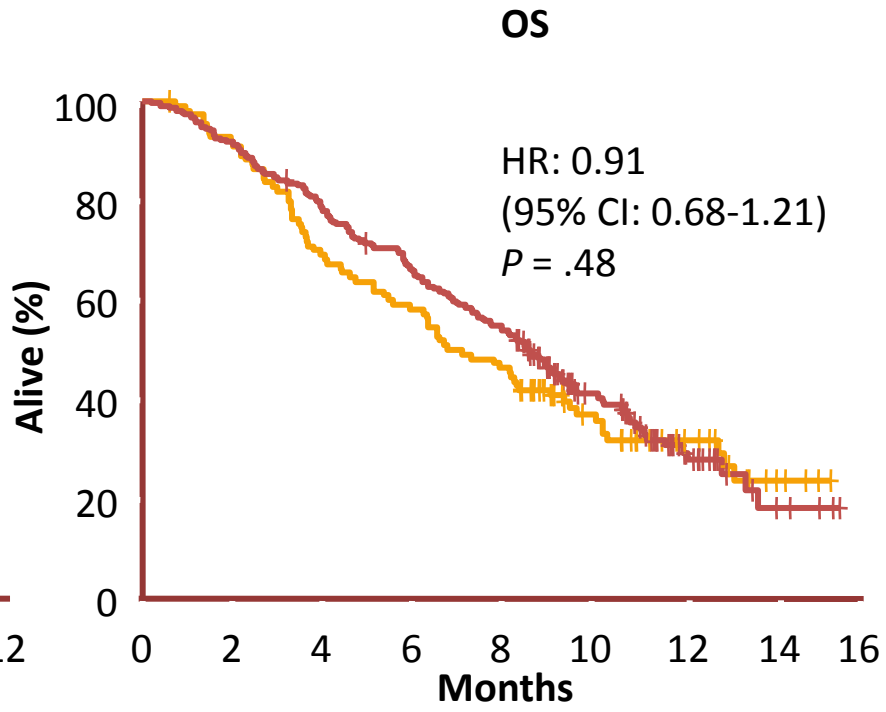


The KRAS protein plays a central role in tumor development, regulating downstream proteins that are involved in proliferation, survival, metastasis and angiogenesis

Cetuximab & CRC: BOND study

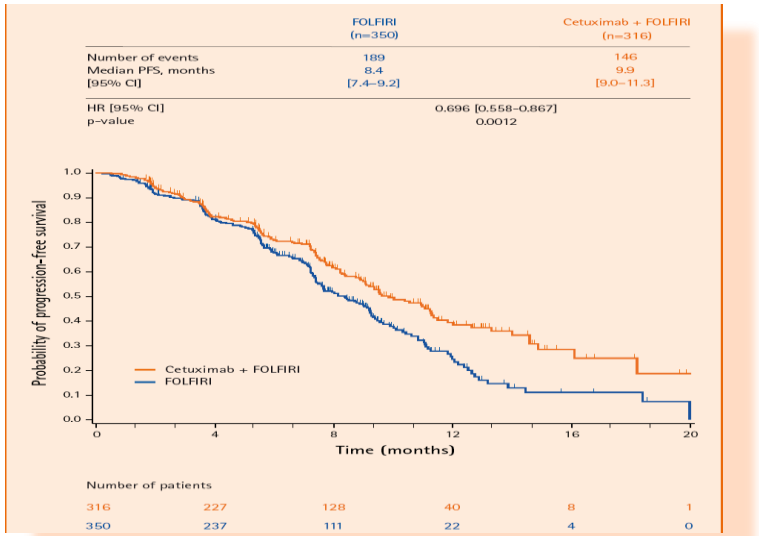
- Addition of cetuximab to irinotecan improved the response rate and time to progression but not overall survival

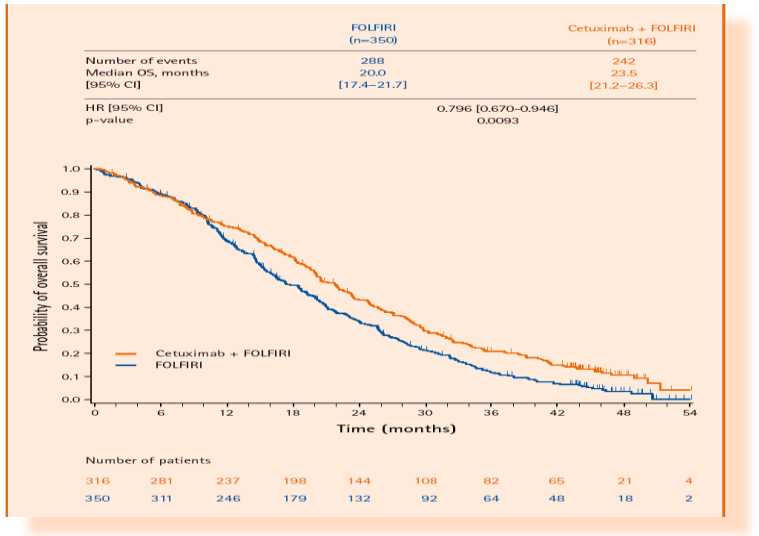




Cunningham D, et al. N Engl J Med. 2004;351:337-345

Cetuximab + FOLFIRI: CRYSTAL study

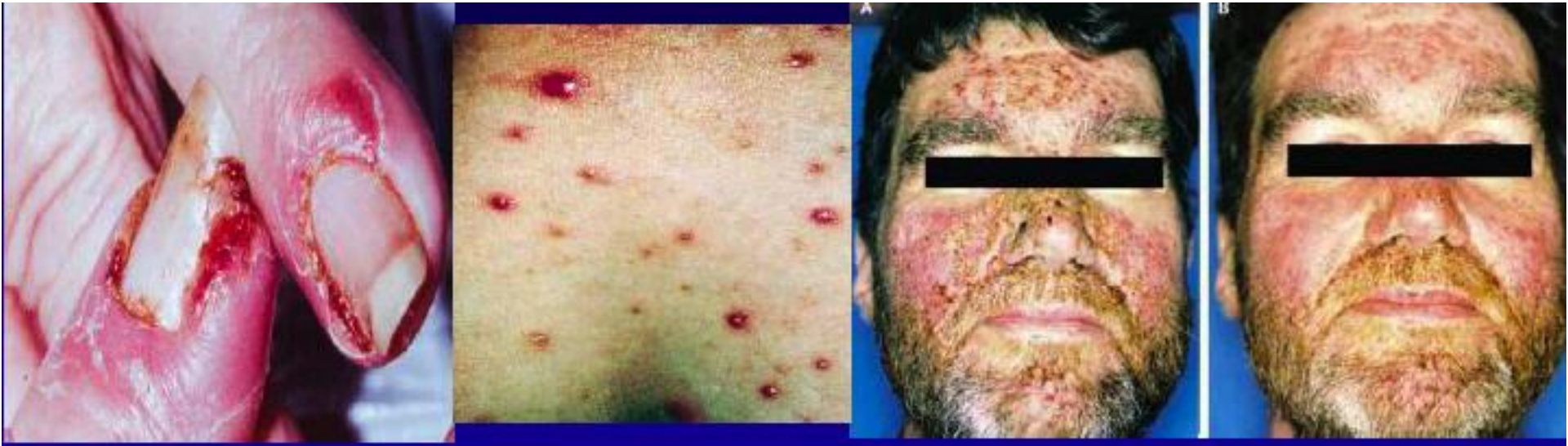




	Cetuximab plus FOLFIRI versus FOLFIRI (n= 666)
OS, months	**23.5 vs 20.0 (HR=0.796; p=0.0093)**
PFS, months	**9.9 vs 8.4 (HR=0.696; p=0.0012)**
ORR, %	**57.3 vs 39.7 (OR=2.0693; p<0.0001)**

Van Cutsem E, et al. N Engl J Med. 2009;360(14):1408-17

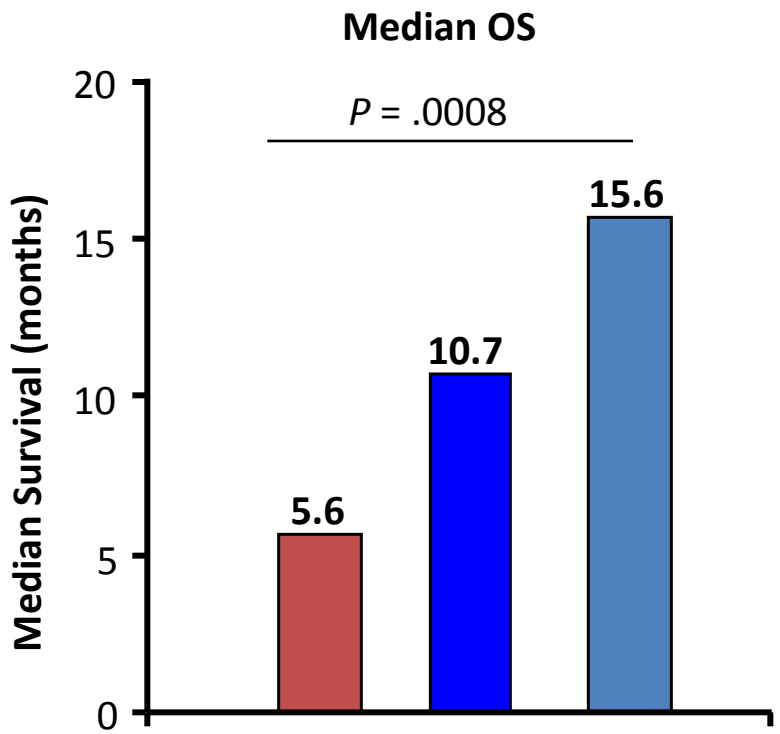
Correlation of skin reaction of Cetuximab and efficacy : BOND subgroup analysis



Grade of skin reaction (up to Week 4)	Percentage of patients	Response rate	mTTP	Median survival
0	14.7	6.3%	1.4 months	3.0 months
1	26.6	8.6%	1.5 months	6.5 months
2	45.4	27.3%	4.2 months	10.3 months
3	13.3	55.2%	8.2 months	13.7 months

Cunningham D NEJM 2004

OS in Iri-Refractory CRC Treated With Cetuximab: *KRAS* and Skin Toxicity



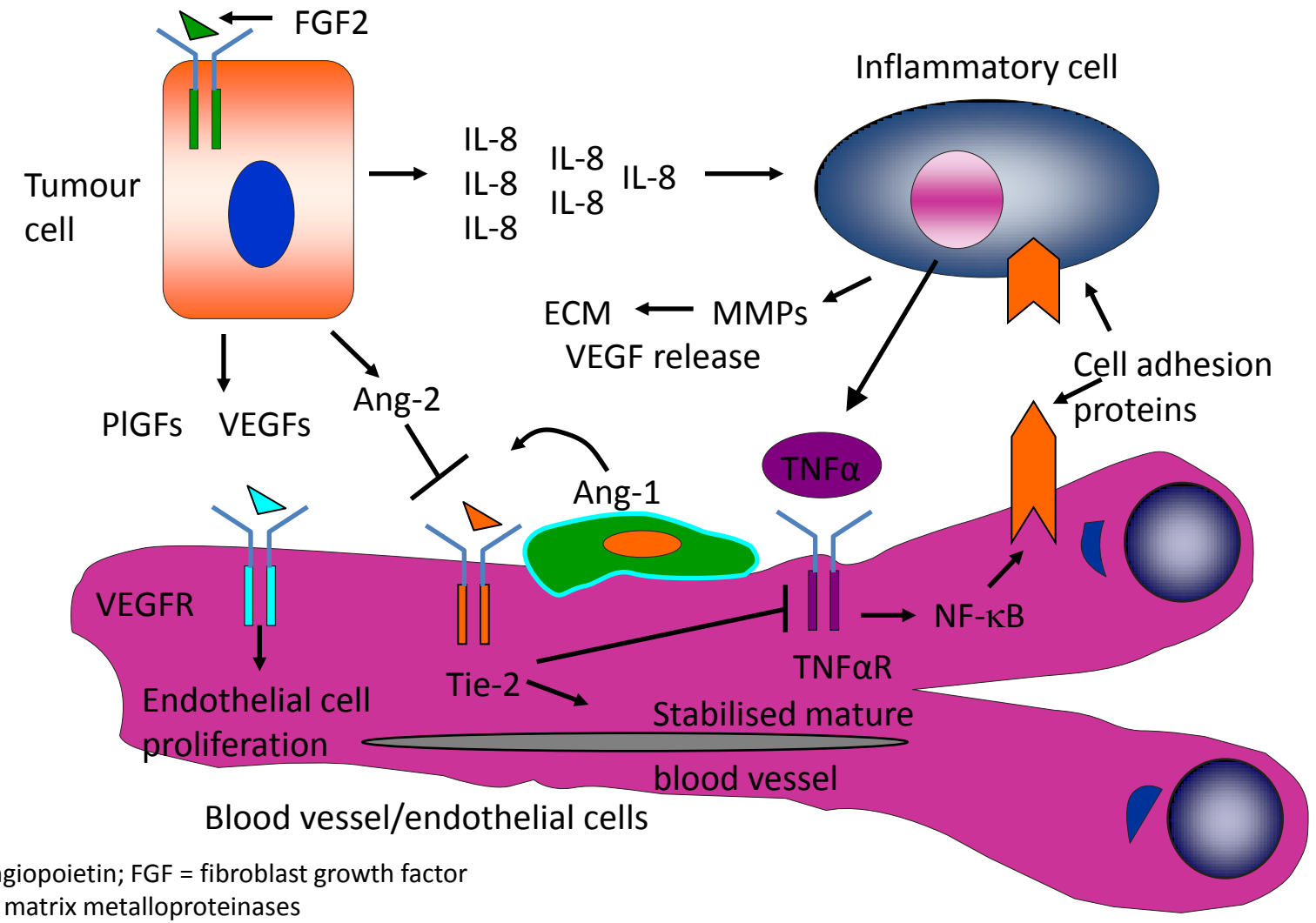
- 0 good prognostic factors (*KRAS* mutation and grade 0-1 skin toxicity)
- 1 good prognostic factors (wild type or grade 2-3 skin toxicity)
- 2 good prognostic factors (wild type and grade 2-3 skin toxicity)

Lièvre A, et al. J Clin Oncol. 2008;26:374-379.

EGFR targeting in CRC

- No correlation between EGFR expression status and antitumor activity of EGFR monoclonal antibodies
- Cetuximab reverses the resistance of colorectal tumors to irinotecan.
- One gene mutation (K-RAS) predicts resistance to anti-EGFR monoclonal antibodies
- There is a correlation between skin reaction to Mab targeting EGFR and treatment outcome

Angiogenesis: a multiple signaling process



Ang = angiopoietin; FGF = fibroblast growth factor
MMPs = matrix metalloproteinases
TNF = tumour necrosis factor; VEGFR = VEGF receptor
PlGF = placental growth factor

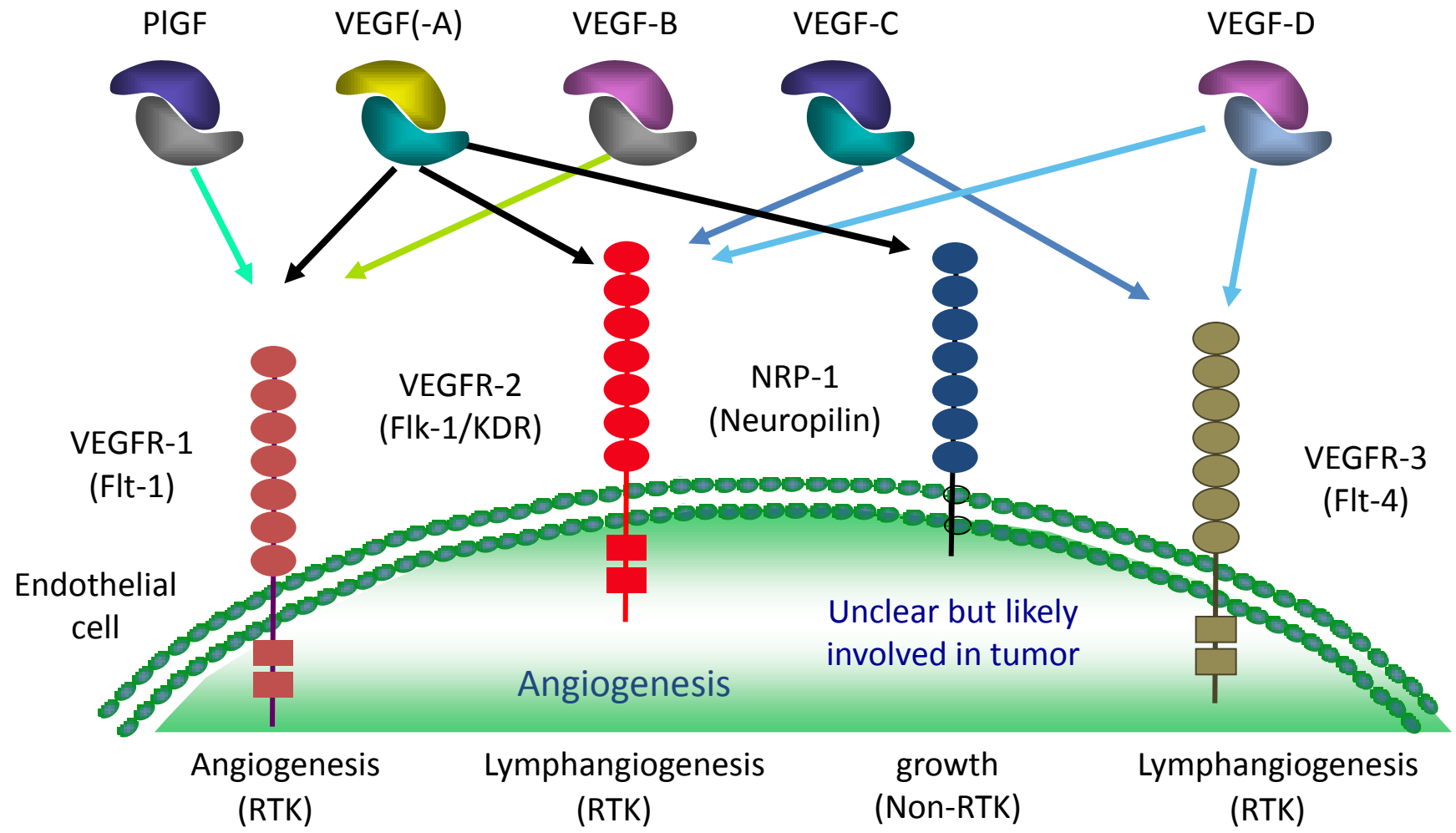
Modified from Acevedo, et al. Cell Cycle 2009

Rationale for targeting VEGF pathway

- VEGF is a central mediator of tumor angiogenesis
  - VEGF inhibition may prevent the growth of new tumor blood vessels
- VEGF is critical for maintaining existing immature tumor vasculature, suggesting its inhibition may lead to vascular regression
- VEGF is overexpressed in a wide variety of tumors and has prognostic implication, thus making it a potential therapeutic target in many tumor types
- Inhibition of VEGF suppresses tumor growth in animal models

Ferrara. J Mol Med 1999; Carmeliet, Jain. Nature 2000

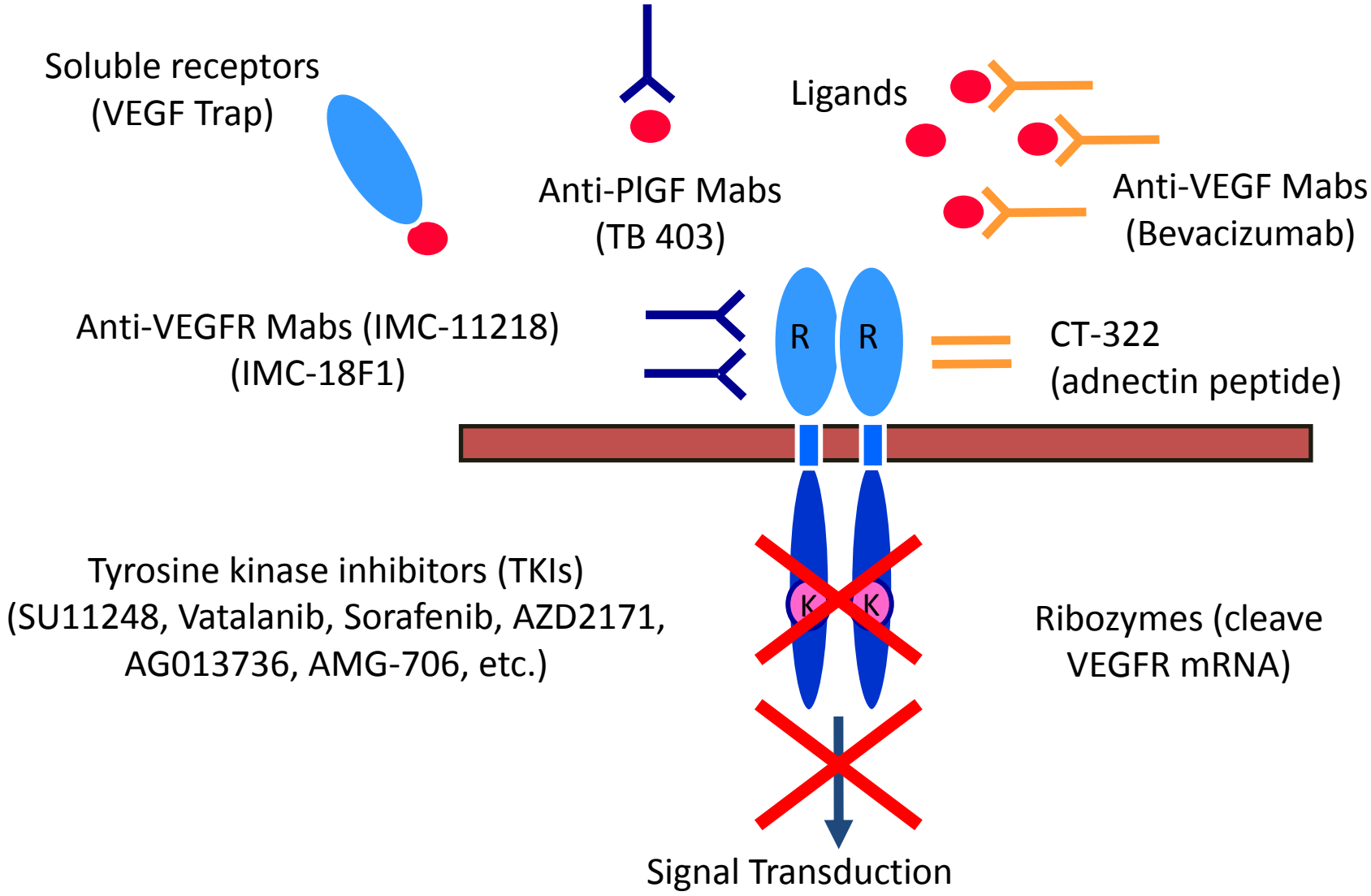
The VEGF family and its receptors



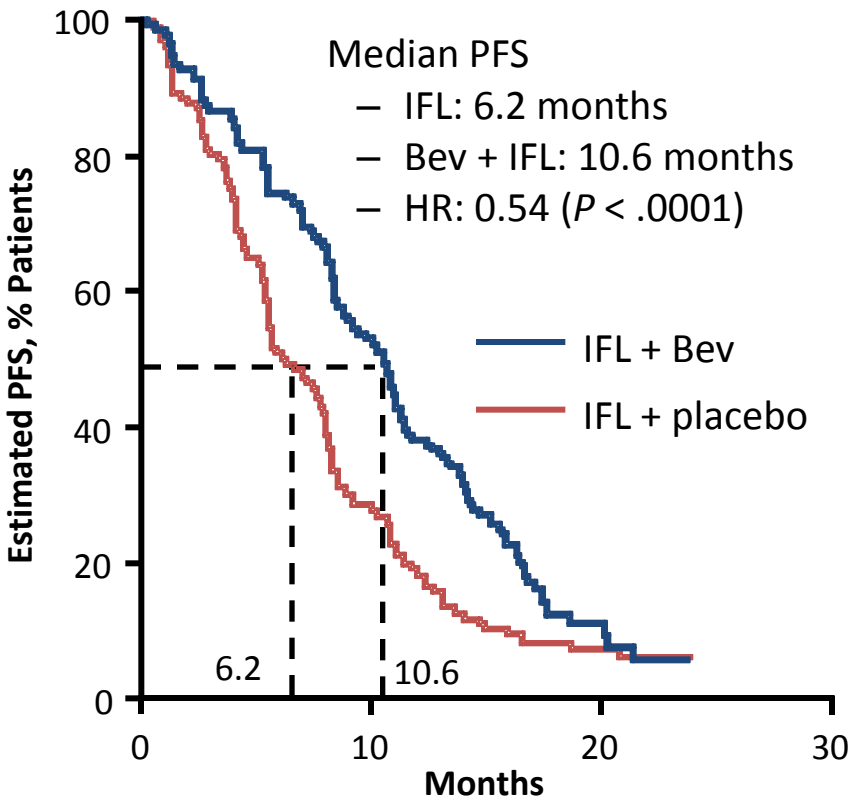
PIGF=placental growth factor
RTK=receptor tyrosine kinase

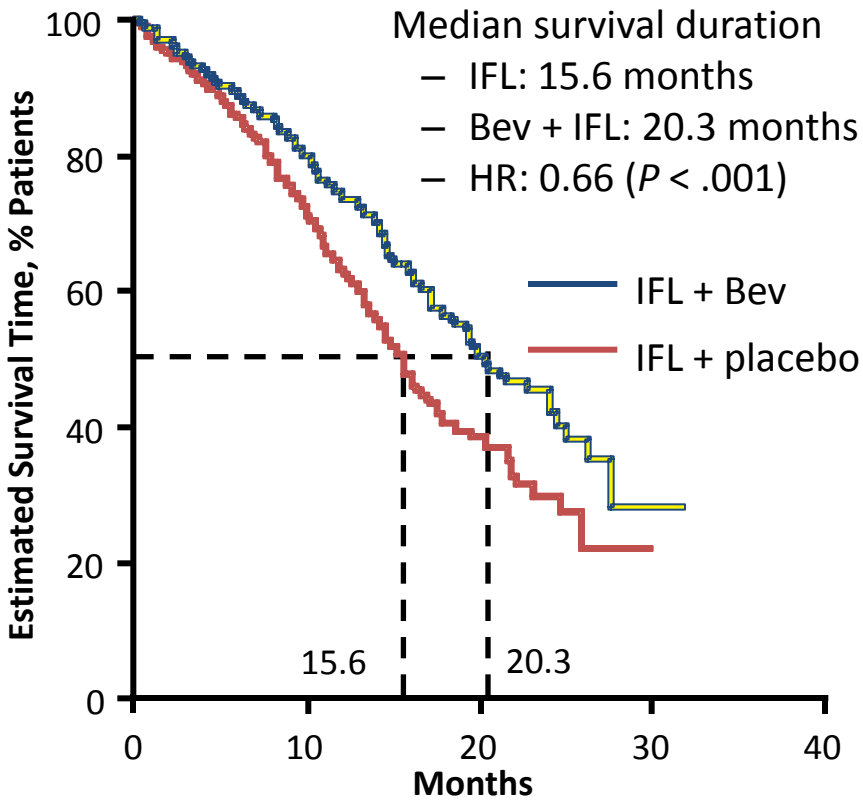
Dvorak. JCO 2002; Ferrara. Nat Med 2003

Anti-VEGF pathway therapies



Bevacizumab + IFL for Metastatic CRC: Phase III AVF2107g Trial

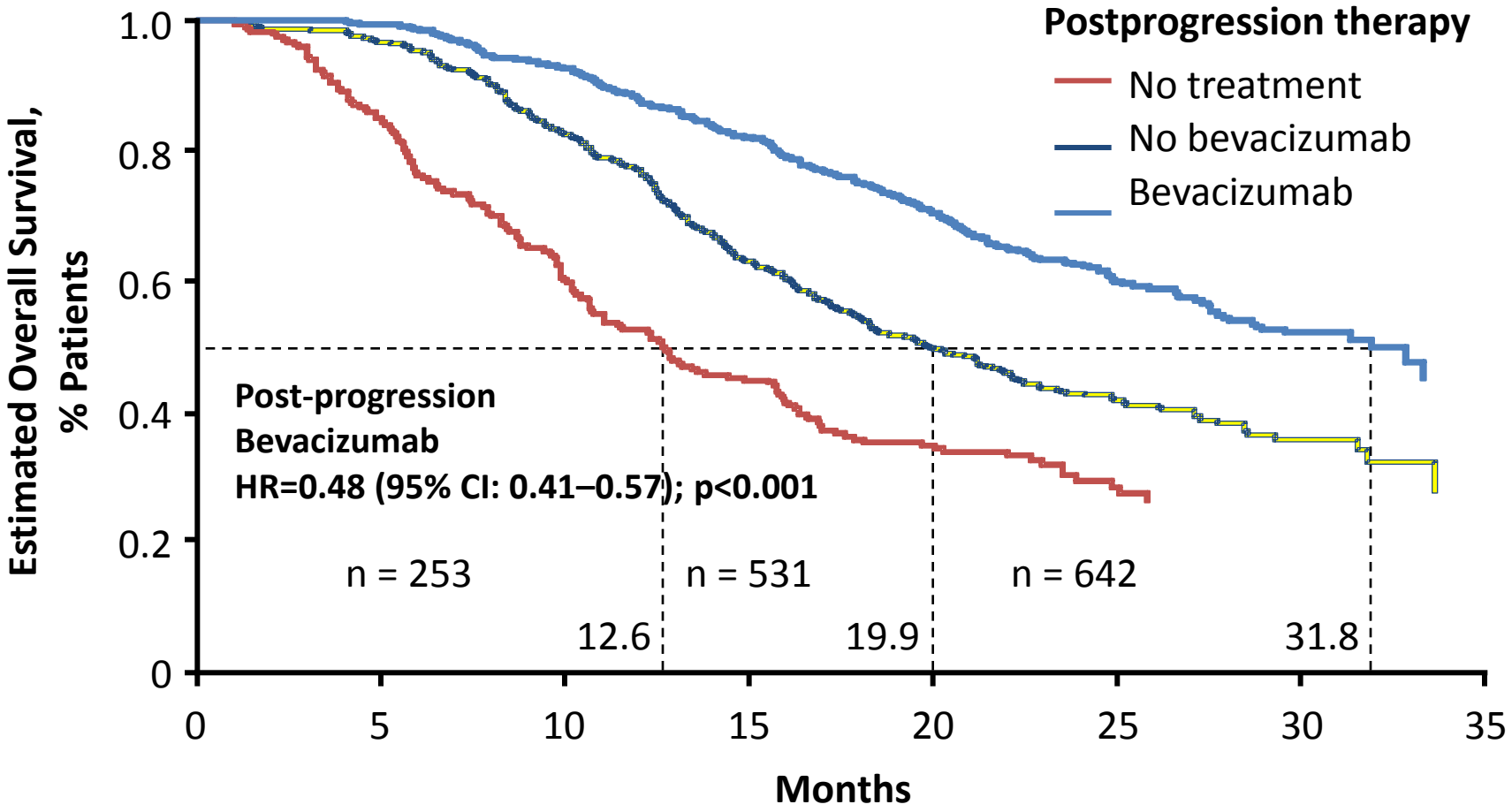




Addition of bevacizumab to first-line combination chemotherapy improves PFS and OS vs IFL alone

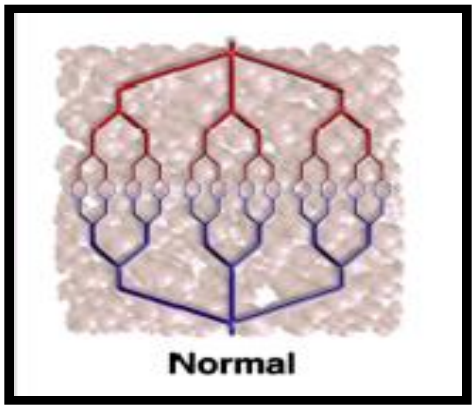
Hurwitz H, et al. N Engl J Med. 2004;350:2335-2342.

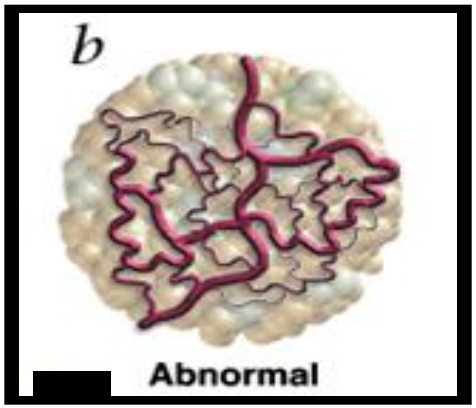
Bevacizumab Increases Survival After First Progression: BRiTE Study



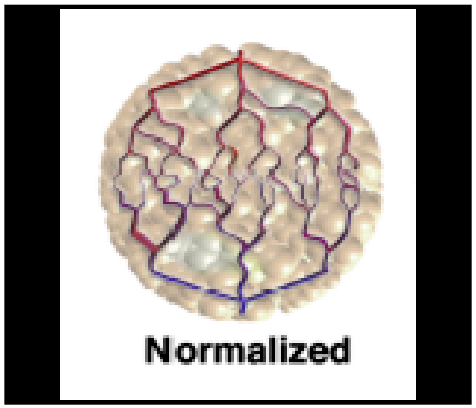
Grothey A, et al. ASCO 2007. Abstract 4036.

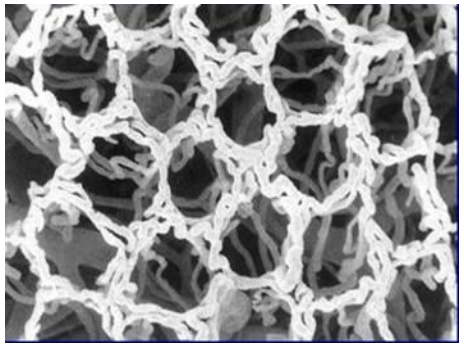
Anti-VEGF antibody 'normalizes' the tumor vasculature

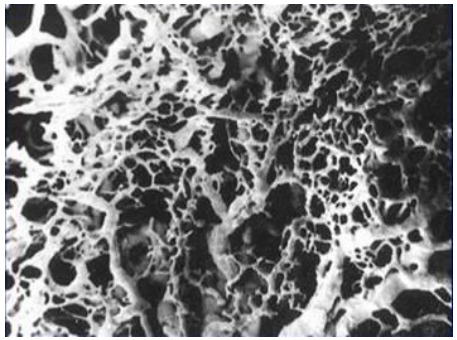




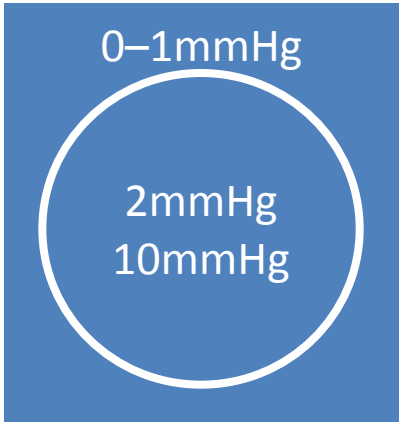
Anti-VEGF



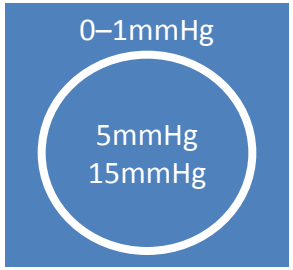




Reduces IFP and MVD and increases drug delivery

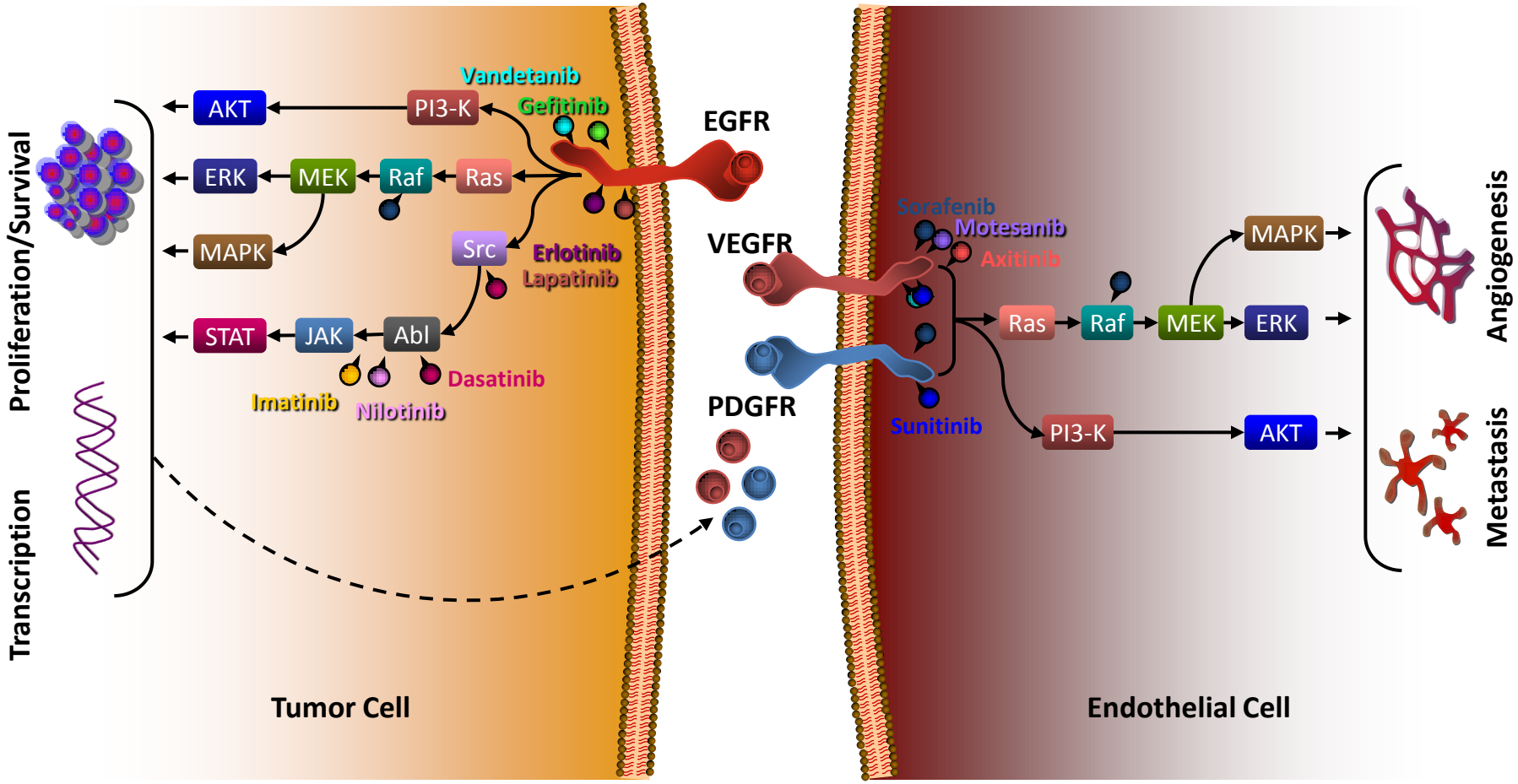


Jain 1988, 1990

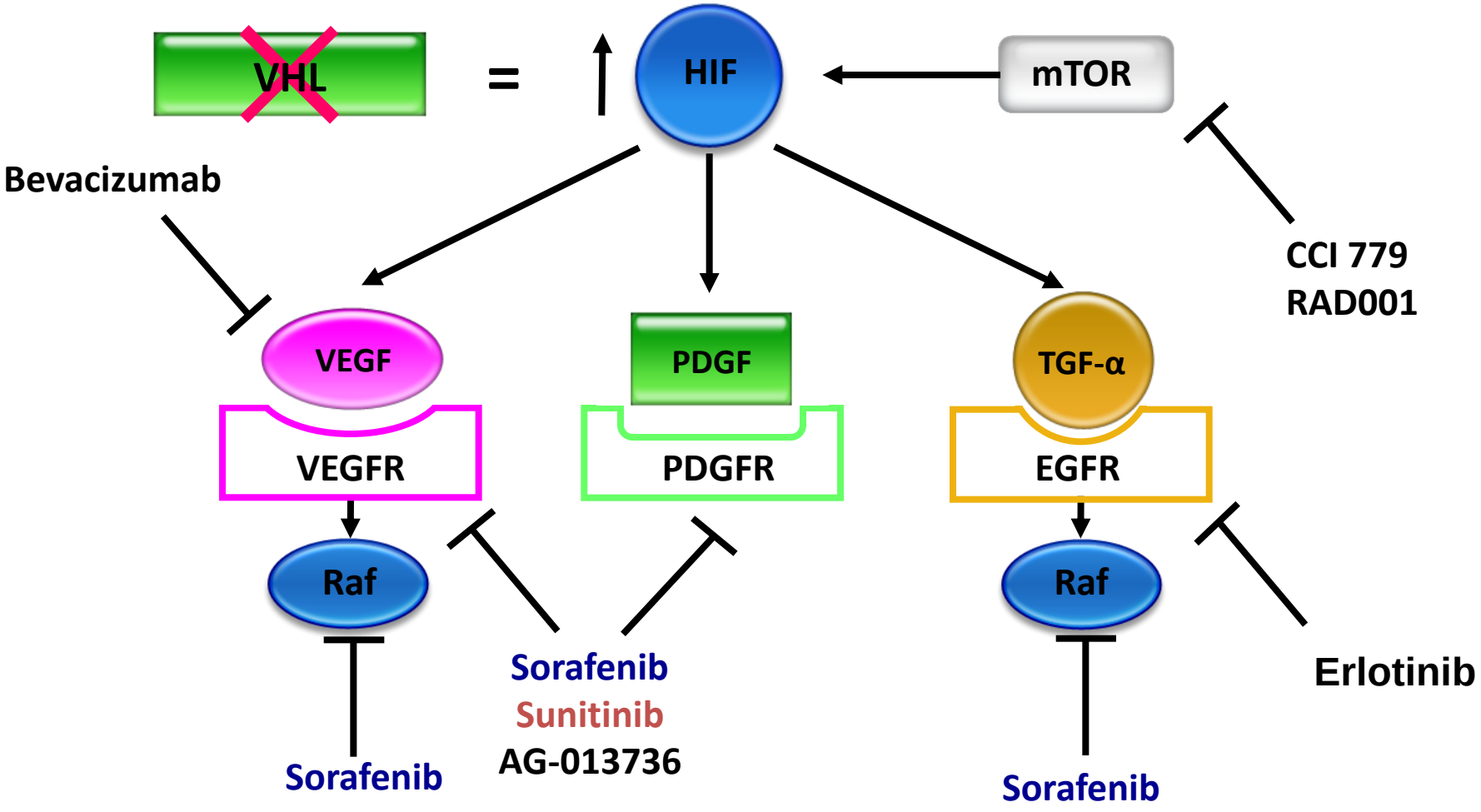


Jain. Nat Med 2001; Willett, et al. Nat Med 2004; Wildiers, et al. Br J Cancer 2003

Intracellular mTKI Targets

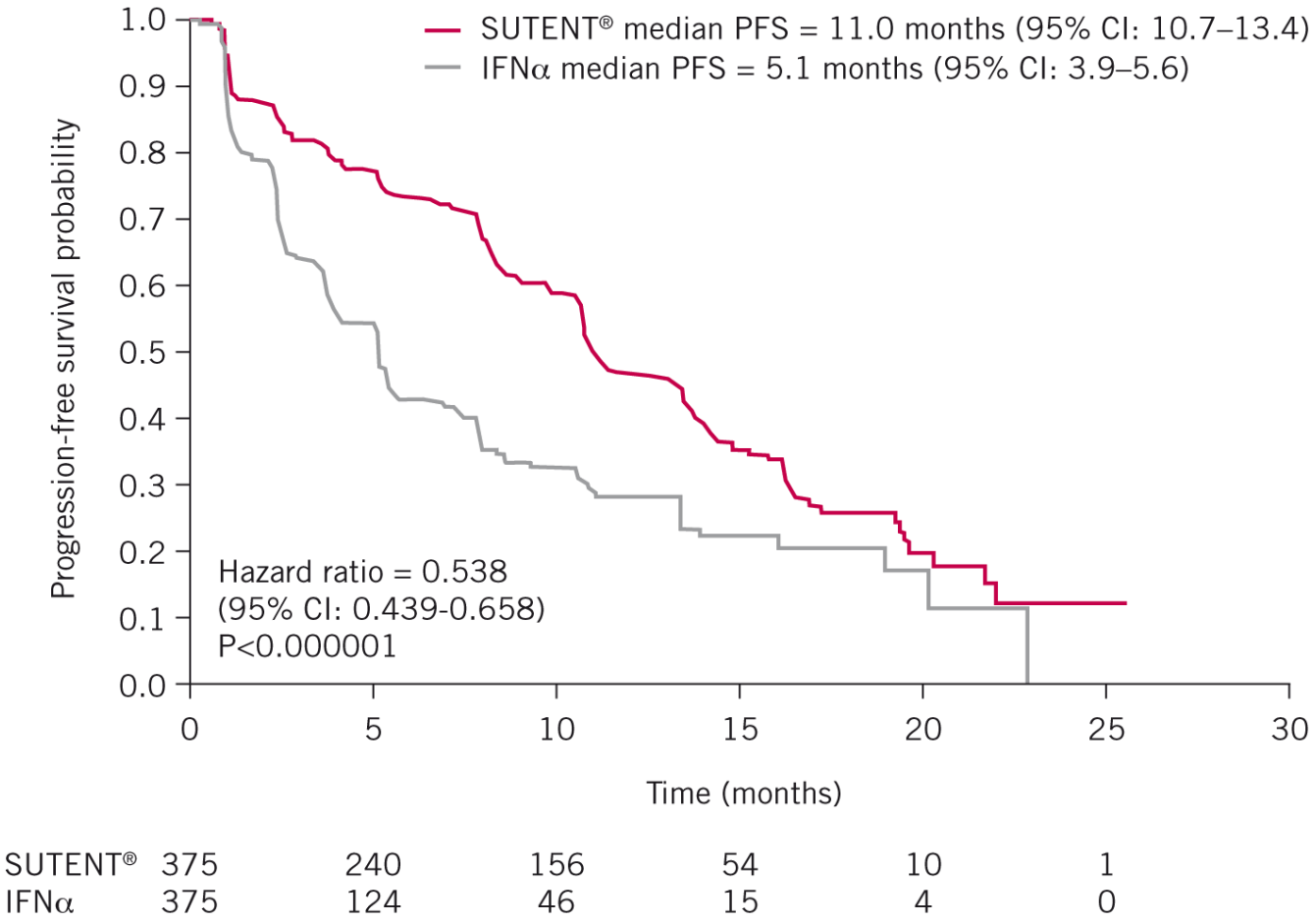


Renal cancer targeted-oriented treatments



Kaelin WG. Nat Rev Cancer 2002;2:673–82

Sunitinib in first-line renal cancer treatment



Motzer RJ *et al. N Engl J Med.* 2007;356:115-124.

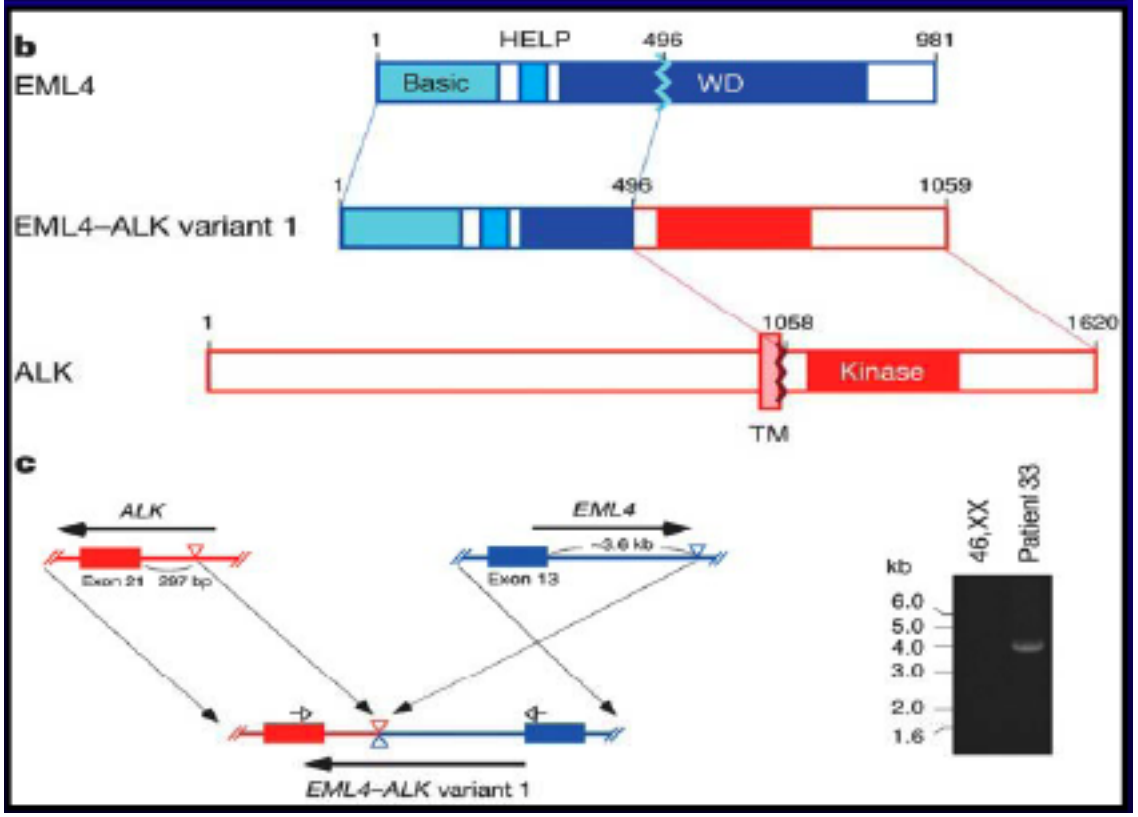
Why to investigate in new angiogenesis inhibitors

- To improve in antiangiogenic therapy
- Evaluate benefit of alternate VEGF inhibition after first-line antiangiogenic failure
- Dual inhibition (more complete pathway inhibition)
- Drugs with oral bioavailability and lower production costs
- Favorable toxicity profile (easy to combine with chemo or other biologic agents)
- To identify biomarkers for efficacy

EML4-ALK fusion in NSCLC

Identification of the transforming *EML4–ALK* fusion gene in non-small-cell lung cancer

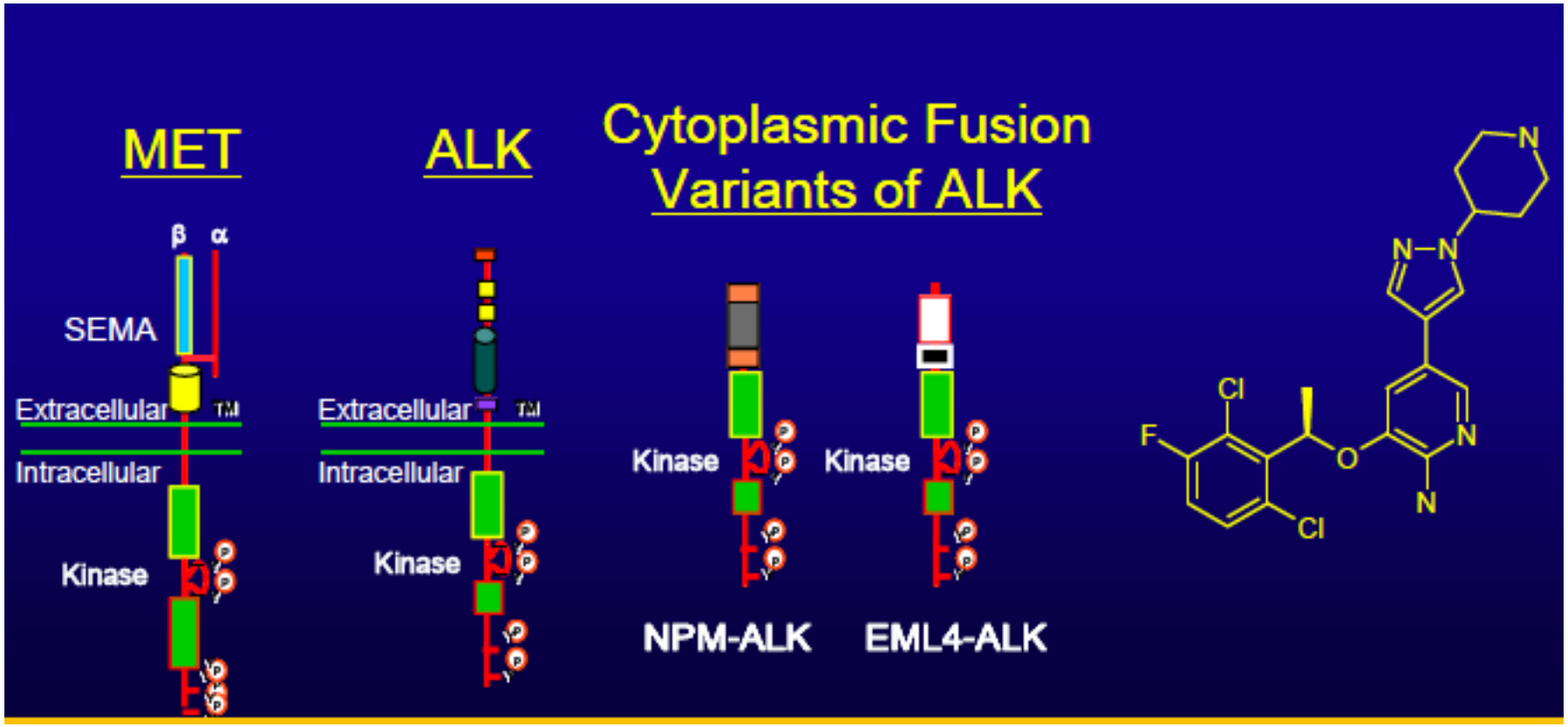
Manabu Soda[1,2], Young Lim Choi[1], Munehiro Enomoto[1,2], Shuji Takada[1], Yoshihiro Yamashita[1], Shunpei Ishikawa[3], Shin-ichiro Fujiwara[1], Hideki Watanabe[1], Kentaro Kurashina[1], Hisashi Hatanaka[1], Masashi Bando[2], Shoji Ohno[2], Yuichi Ishikawa[6], Hiroyuki Aburatani[5,7], Toshiro Niki[3], Yasunori Sohara[4], Yukihiko Sugiyama[2] & Hiroyuki Mano[1,7]



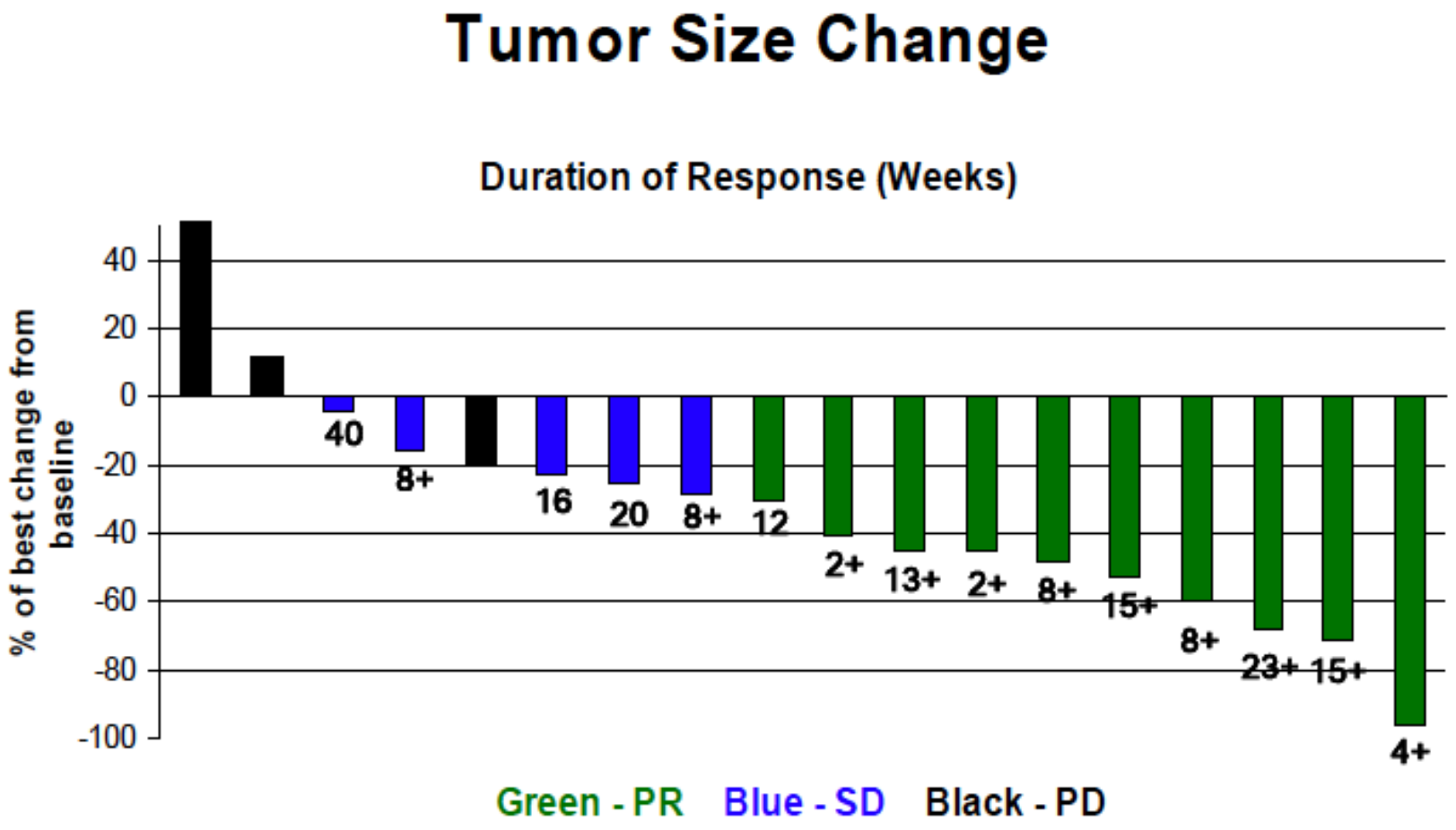
EML4-ALK
Frequency:
Adenocarcinoma = 4% (26/662)
At least 7 fusion variants

Nature 448; 561 (2007)

PF-0241066 a selective oral inhibitor of MET and ALK kinases

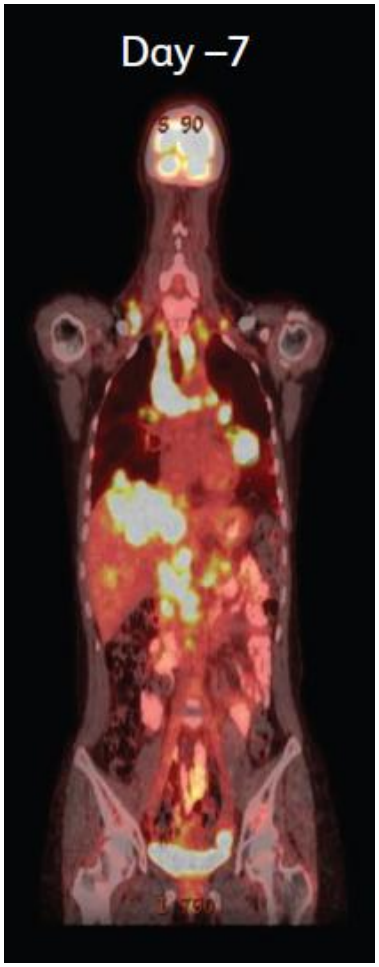


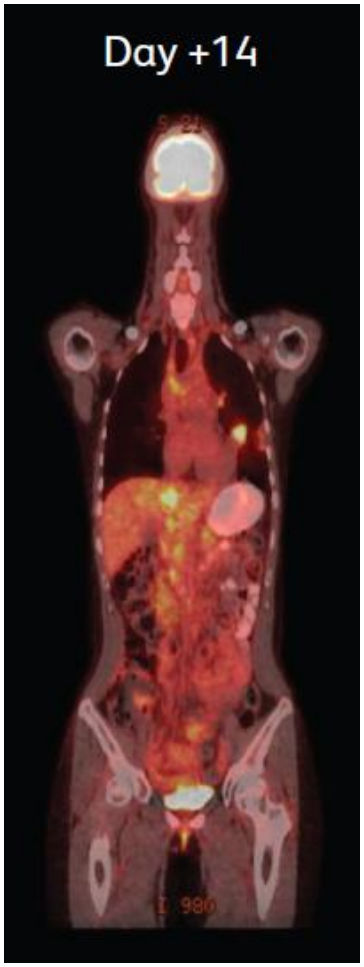
Tumor Responses to PF-02341066 for NSCLC evaluable patients with ALK fusions

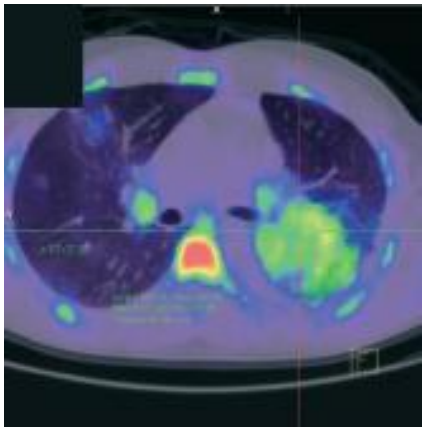


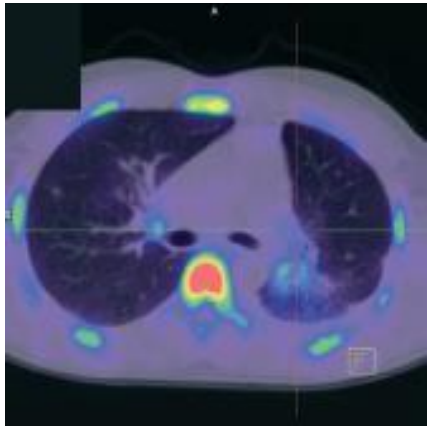
One patient had clinical progression and discontinued without radiographic confirmation.

Response to Crizotinib Occurs Rapidly



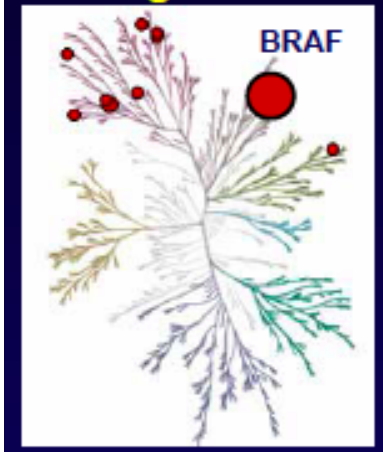






PLX4032: novel, small molecule inhibitor. Selectivity for BRAFV600E in vitro and in vivo

Selective for *BRAF*^{V600E} kinase among 70 kinases screened



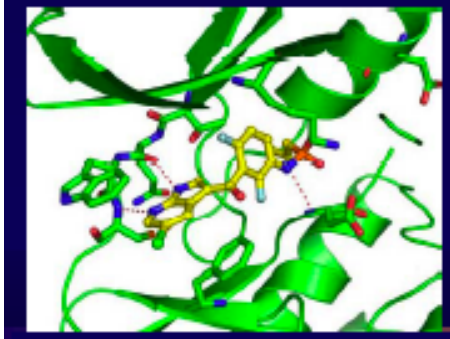
IC_{50} (nM)

- 10–100
- 100–1000
- 1000–10000

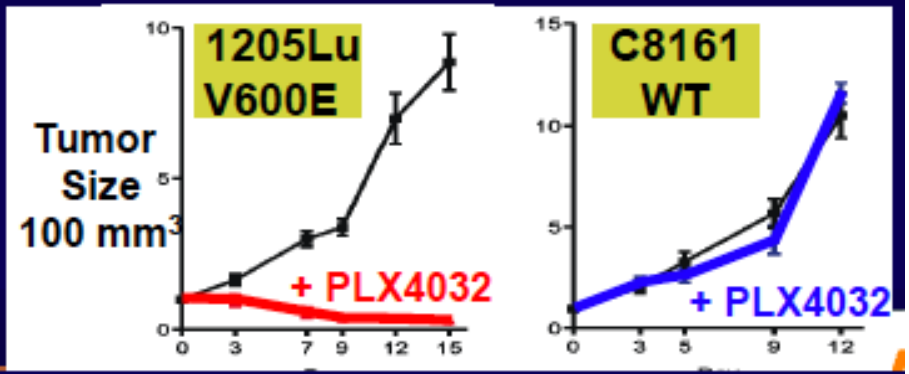
Selective in cellular assays

	Phospho-ERK	IC_{50} (nM)
V600E	A375	20
	COLO829	10
	COLO205	30
WT	SW620	>40,000
	SKMEL2	14,000

Kinase domain binding

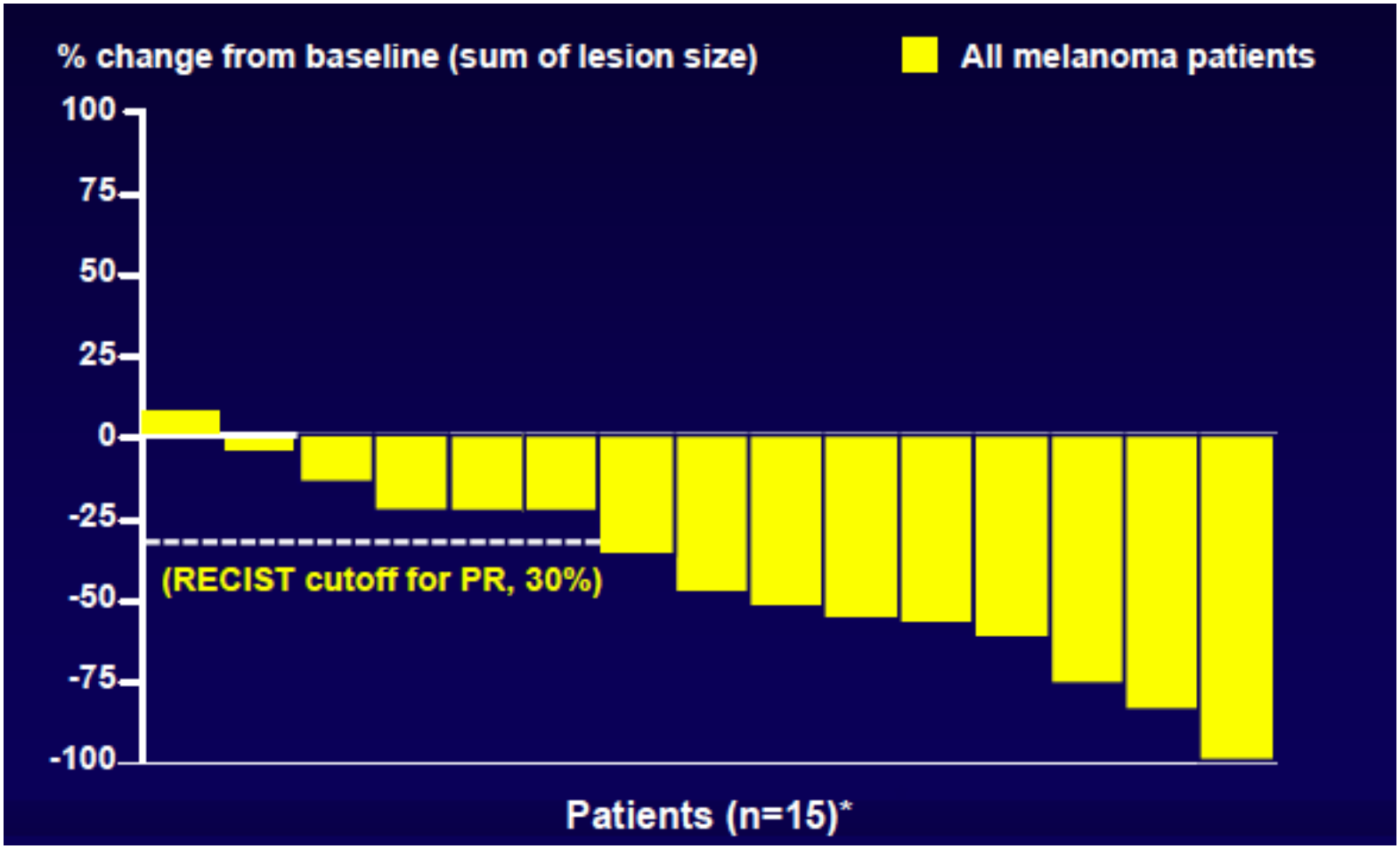


Selective regression of V600E tumors

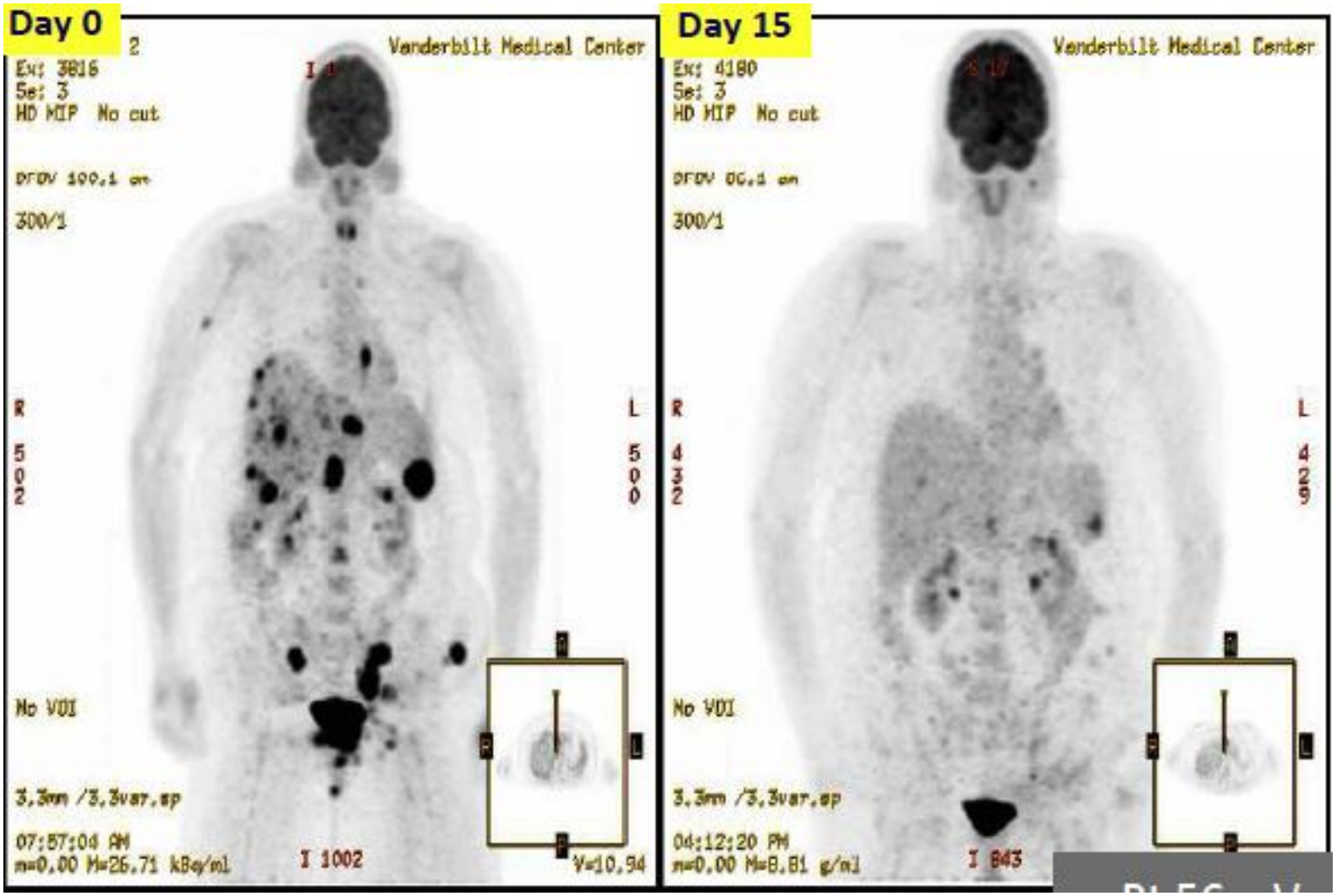


PLX4720 co-structure with kinase domain of BRAFV600E (Tsai J et al. 2008 PNAS)

BRAFV600E melanoma patients treated with PLX4032 > 240 mg BID



BRAFV600E melanoma patient PET scan at baseline and day +15 after PLX4032 treatment at 720 mg BID

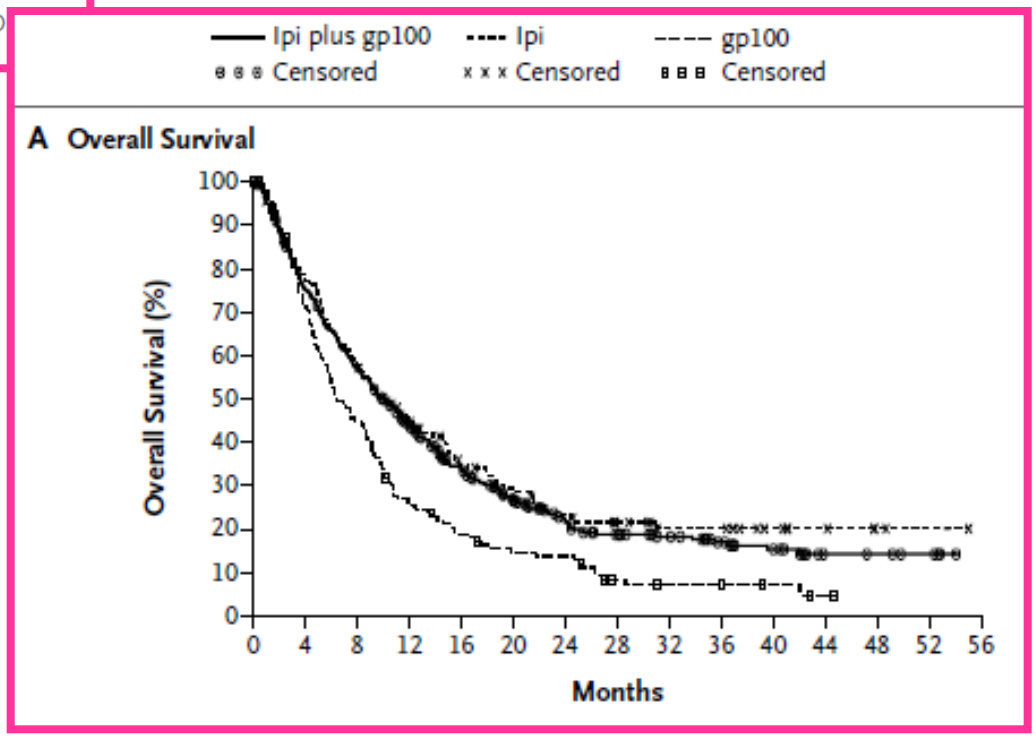


Melanoma immune therapy

ORIGINAL ARTICLE

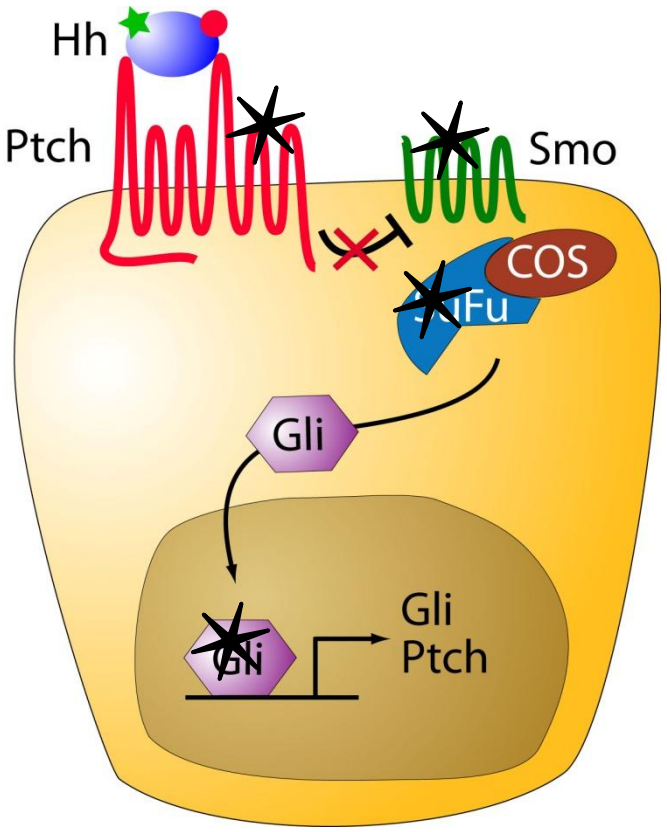
Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

F. Stephen Hodi, M.D., Steven J. O'Day, M.D., David F. McDermott, M.D., Robert W. Weber, M.D., Jeffrey A. Sosman, M.D., John B. Haanen, M.D., Rene Gonzalez, M.D., Caroline Robert, M.D., Ph.D., Dirk Schadendorf, M.D Jessica C. Hassel, M.D., Wallace Akerley, M.D.,

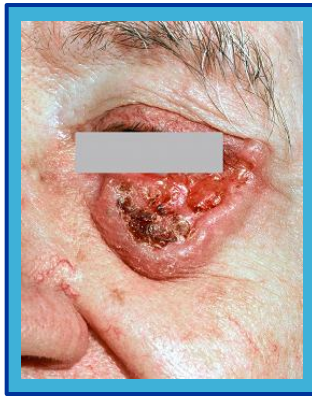


Hodi FS, et al. N Engl J Med 2010;363(8):711-23

Activation of the Hedgehog Pathway through Mutations in PTCH or Smo Causes Cancer



Brain cancer
(Medulloblastoma)



Skin cancer
(Basal Cell Carcinoma)

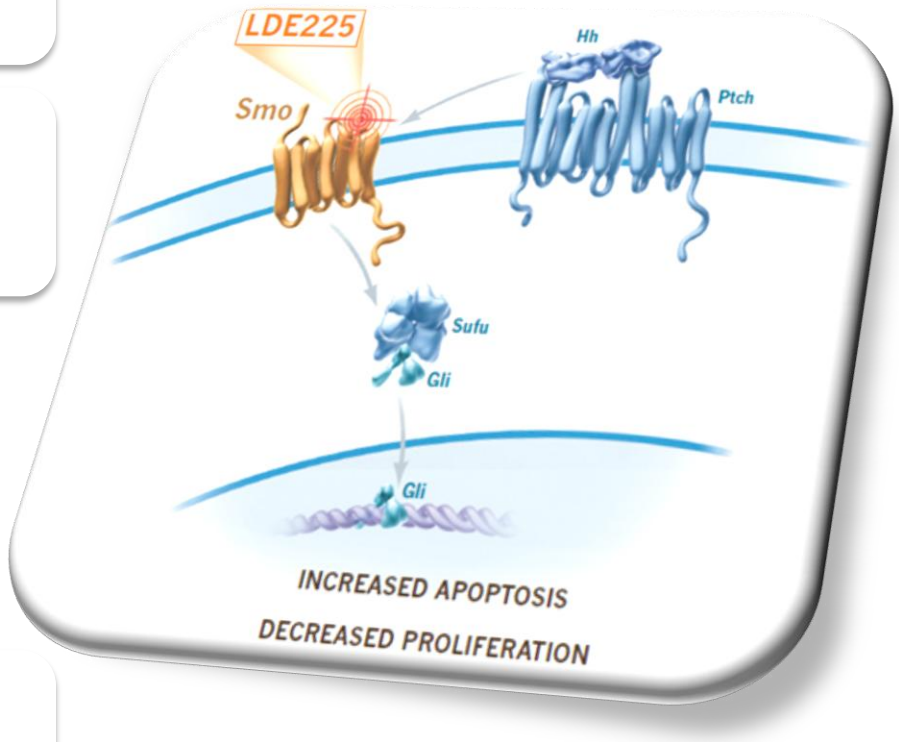
LDE225: Selective Inhibitor of Smoothened (Smo) From Novel Structural Class

Smo (GPCR-like) positively regulates Hedgehog (HH) signal transduction; leading to cell proliferation and differentiation

Genetic activation of the HH pathway at or upstream of Smo is linked to tumorigenesis of certain cancers

- 20% of sporadic human medulloblastoma
- >70% of basal cell carcinomas
- Upregulation of HH pathway without known mutations is also linked to additional tumor types (pancreatic and lung, and well as some hematological malignancies)

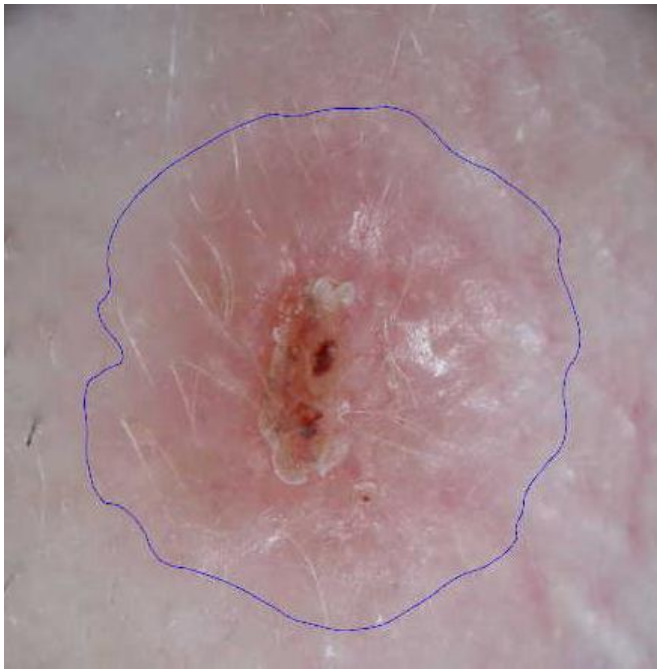
Potently inhibits HH- and Smo- dependent proliferation *in vivo* in preclinical studies

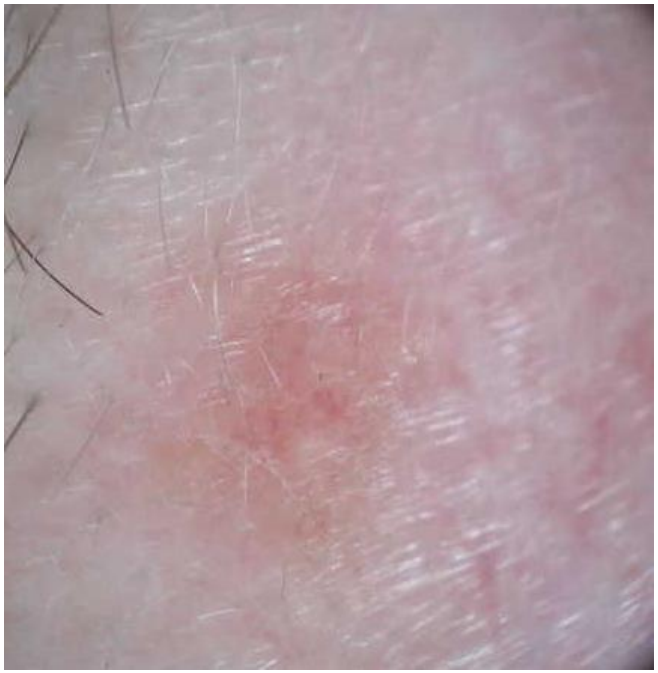


1. Pasca di Magliano M, Hebrok M. *Nature*. 2003;**3**:903–911.
2. McMahon AP, Ingham PW, Tabin CJ. *Curr Top Dev Biol*. 2003;**53**:1–114.
3. Reifenberger J, Wolter M, Knobbe B, *et al*. *Br J Dermatol*. 2005;**152**:43–51.

BCC in Gorlin Syndrome

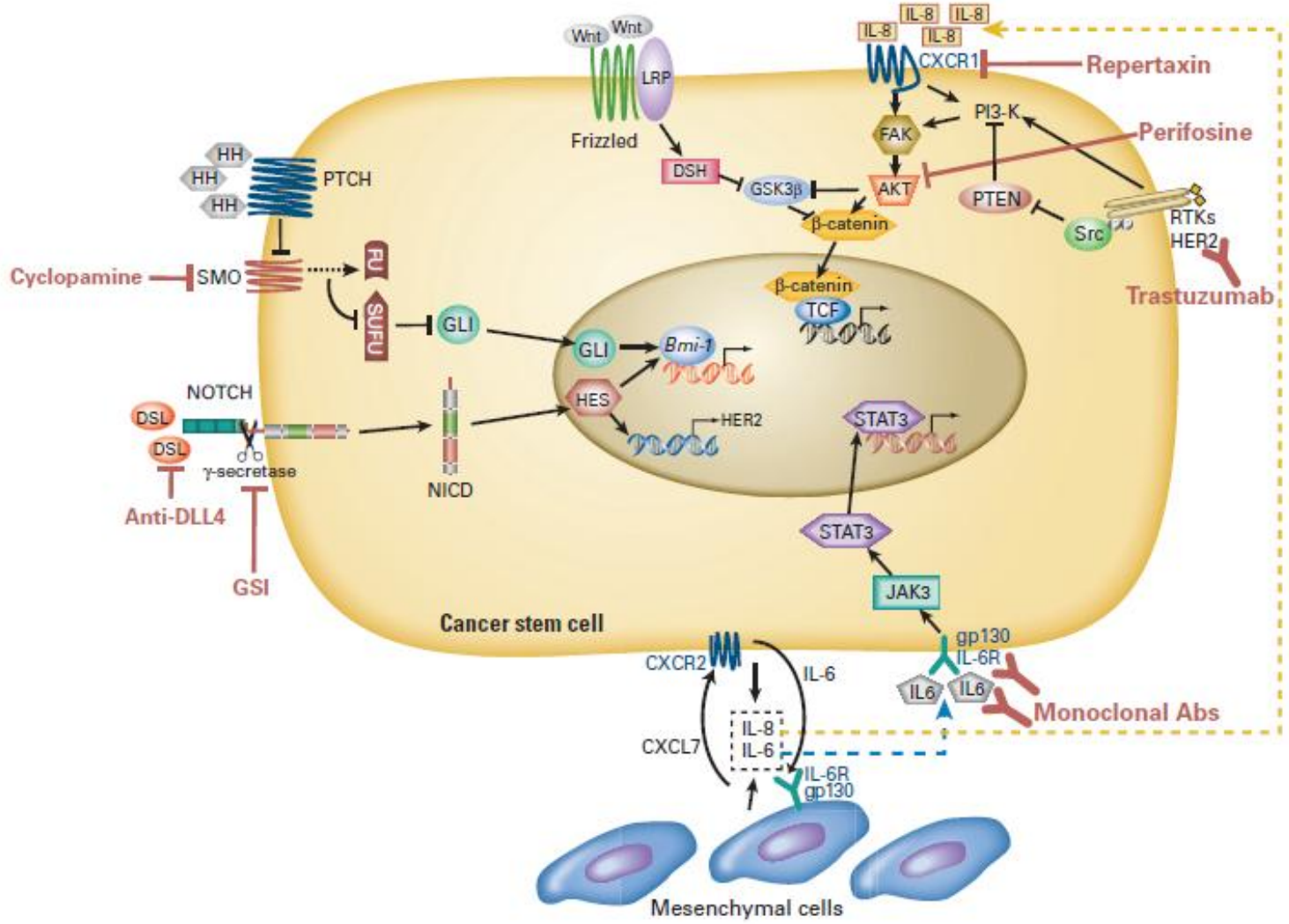
Response to topical LDE225





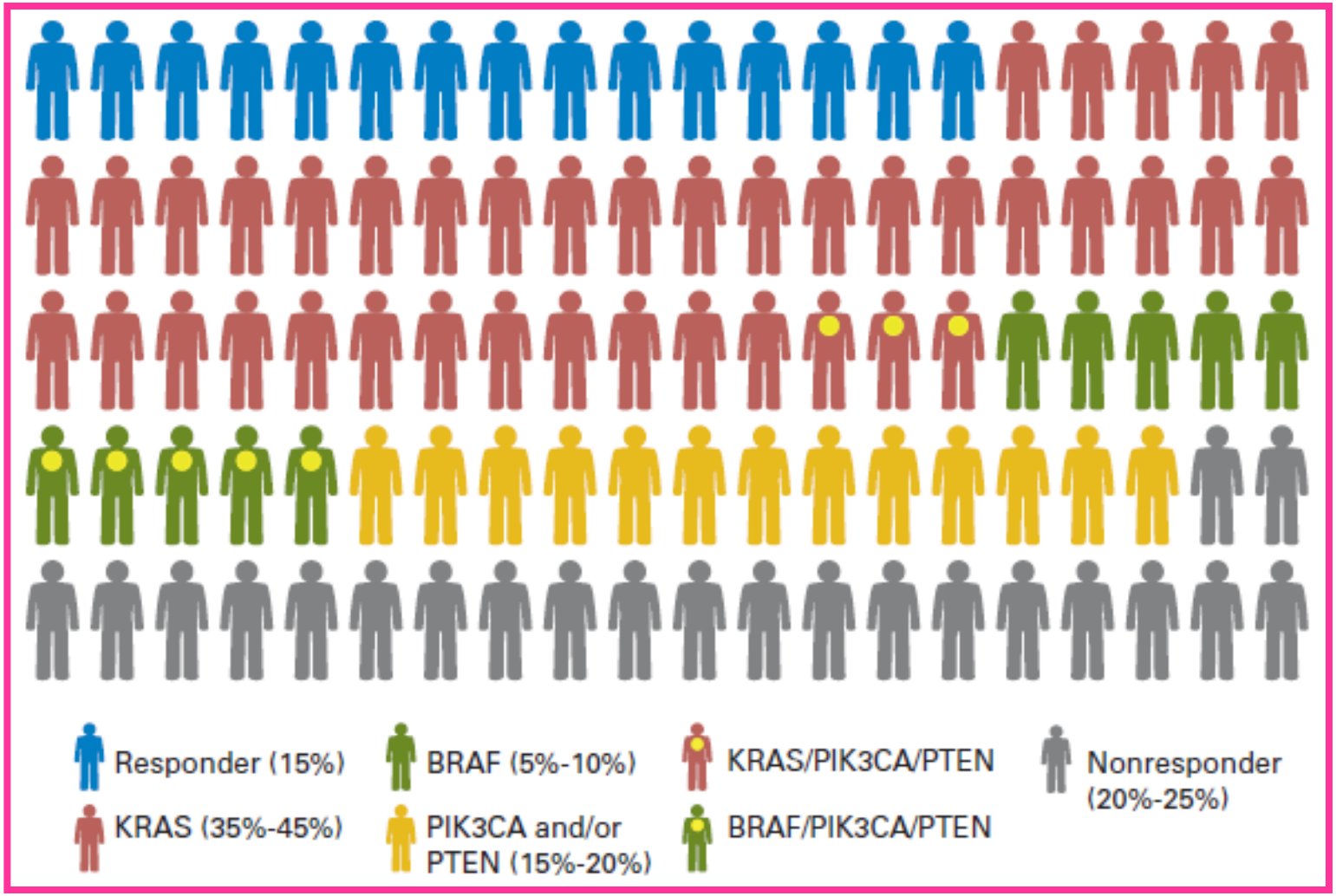
- **Baseline** (11Aug2009)
- **End of Tx** (9Sep2009)

Stem-Cell targets



Liu S and Micha MS. J Clin Oncol 2010;28:4006-4012

Personalized treatment



Bardelli et al. J Clin Oncol. 2010;28(7):1254-61

New drugs development in 2011: A break with the past

- Patient: Tumor, CTC, bone marrow tumor cells, SNPs,…
- Lab: basic and translational research
- Industry: development of drugs with selectivity and good safety
- Early « individualization » of new drug development based on the target, drug and patient characteristics
- Aim: Physicians select prescription based upon
  - Individual genomic/proteomic testing
  - Drug that is active in that patient
  - Drug that is safe in that patient

A multidisciplinary approach and molecular pathology are changing cancer patients management

- Right patient
- Right tumor
- Right drug
- Right time

- Increased efficacy
- Improved safety
- Decreased Cost


¡Muchas
gracias!