PANORAMA DE LOS INHIBIDORES DE TIROSIN-KINASAS (ITKs)

TROBADA DE FARMACÈUTICS DE CATALUNYA
Reunió conjunta de zona SEFH - Catalunya i SCFC

17 de Mayo del 2014

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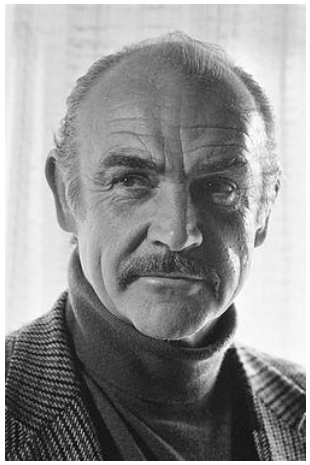
Relación de contenidos

1. **Historia**
2. **Receptores de tirosin-kinasa**
3. **Resistencias**
4. **Fármacos**
5. **Efectos adversos**
6. **Precauciones**

HISTORIA

Historia



Años 40

Años 90

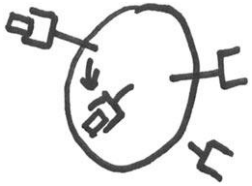
Quimioterapia clásica

Terapia dirigida

Paul Ehrlich: Birth of Targeted Therapy

(1) Antibodies: Nobel Prize for serum therapy in 1908
(2) Targeted chemotherapy: 1910-1911

Receptors on cells



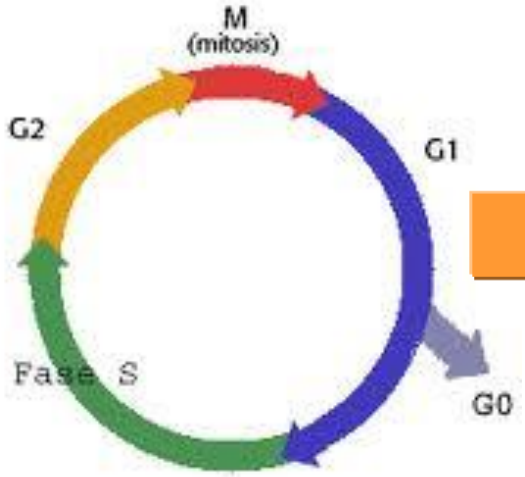
Postulated "side-chains," or "receptors" specific for external substances (dyes), antigens, and nutrients

A bacterial toxin *and* a targeted chemotherapy

Model: bifunctional agent, containing a chemical structure that binds to the "receptor" linked to a toxic molecule

Fig 1. Ehrlich's magic bullet.

Historia



Años 40

Quimioterapia clásica

Años 90

Terapia dirigida

Historia

Table 1. Singular Discoveries and Major Events in the Cancer Field and Changing Relative Survival Rates for Patients with Cancer in the United States, 1863–2006.*

Year	Discovery or Event	Relative Survival Rate
1863	Cellular origin of cancer (Virchow)	
1889	Seed-and-soil hypothesis (Paget)	
1914	Chromosomal mutations in cancer (Boveri)	
1937	Founding of NCI	
1944	Transmission of cellular information by DNA (Avery)	
1950	Availability of cancer drugs through Cancer Chemotherapy National Service Center	
1953	Report on structure of DNA	35%
1961	Breaking of the genetic code	
1970	Reverse transcriptase	
1971	Restriction enzymes Passage of National Cancer Act	
1975	Hybridomas and monoclonal antibodies Tracking of cancer statistics by SEER program	50%
1976	Cellular origin of retroviral oncogenes	
1979	Epidermal growth factor and receptor	
1981	Suppression of tumor growth by p53	
1984	G proteins and cell signaling	
1986	Retinoblastoma gene	
1990	First decrease in cancer incidence and mortality	
1991	Association between mutation in APC gene and colorectal cancer	
1994	Genetic cancer syndromes Association between *BRCA1* and breast cancer	
2000	Sequencing of the human genome	
2002	Epigenetics in cancer MicroRNAs in cancer	
2005	First decrease in total number of deaths from cancer	68%
2006	Tumor stromal interaction	

* Data are from the National Cancer Institute (NCI) Survival, Epidemiology, and End Results (SEER) program. APC denotes adenomatous polyposis coli.

De vita VT & Rosenberg SA. Two hundred years of cancer research. NEJM 2012;366 (23):2207-14

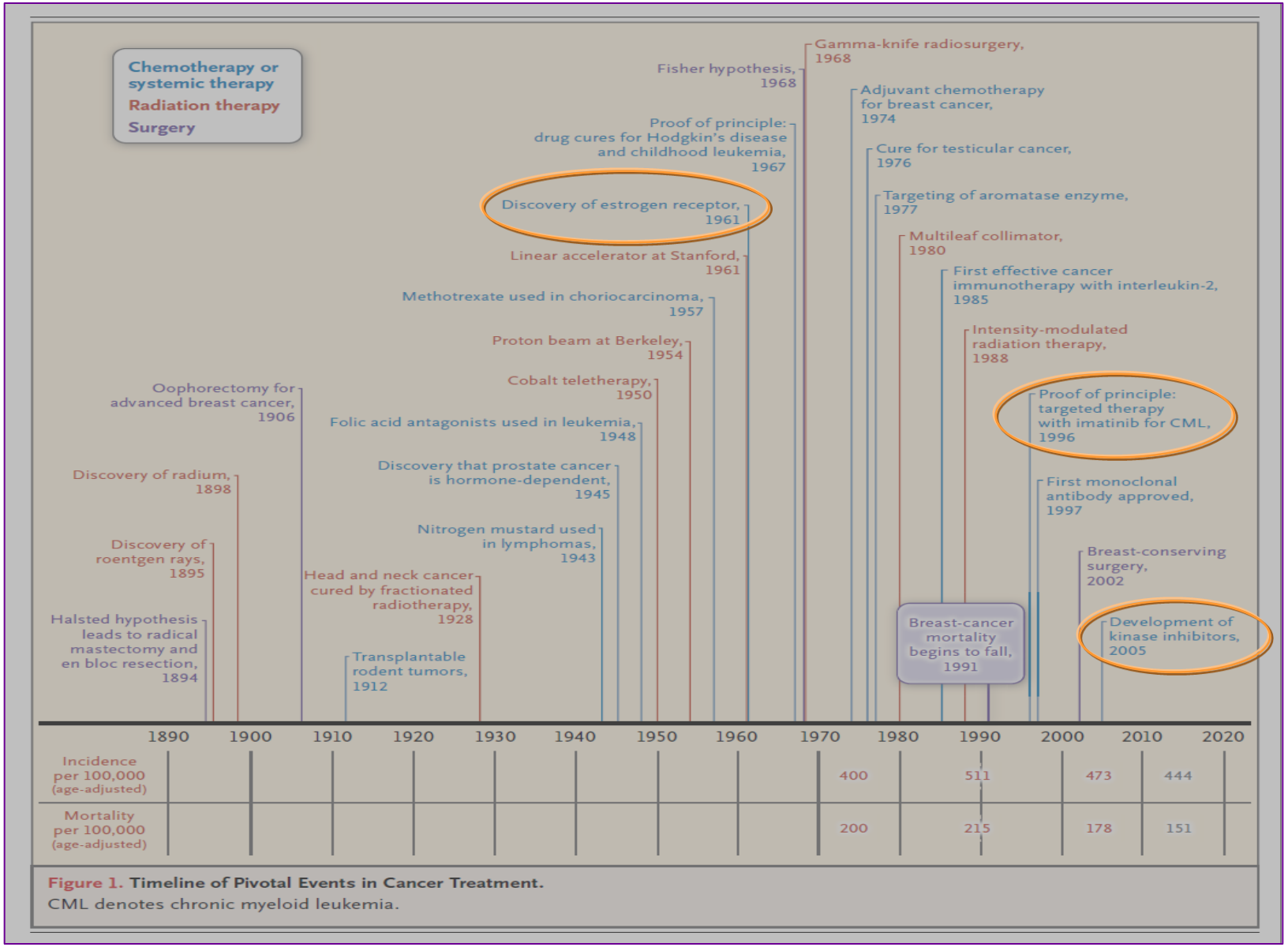


Figure 1. Timeline of Pivotal Events in Cancer Treatment.
CML denotes chronic myeloid leukemia.

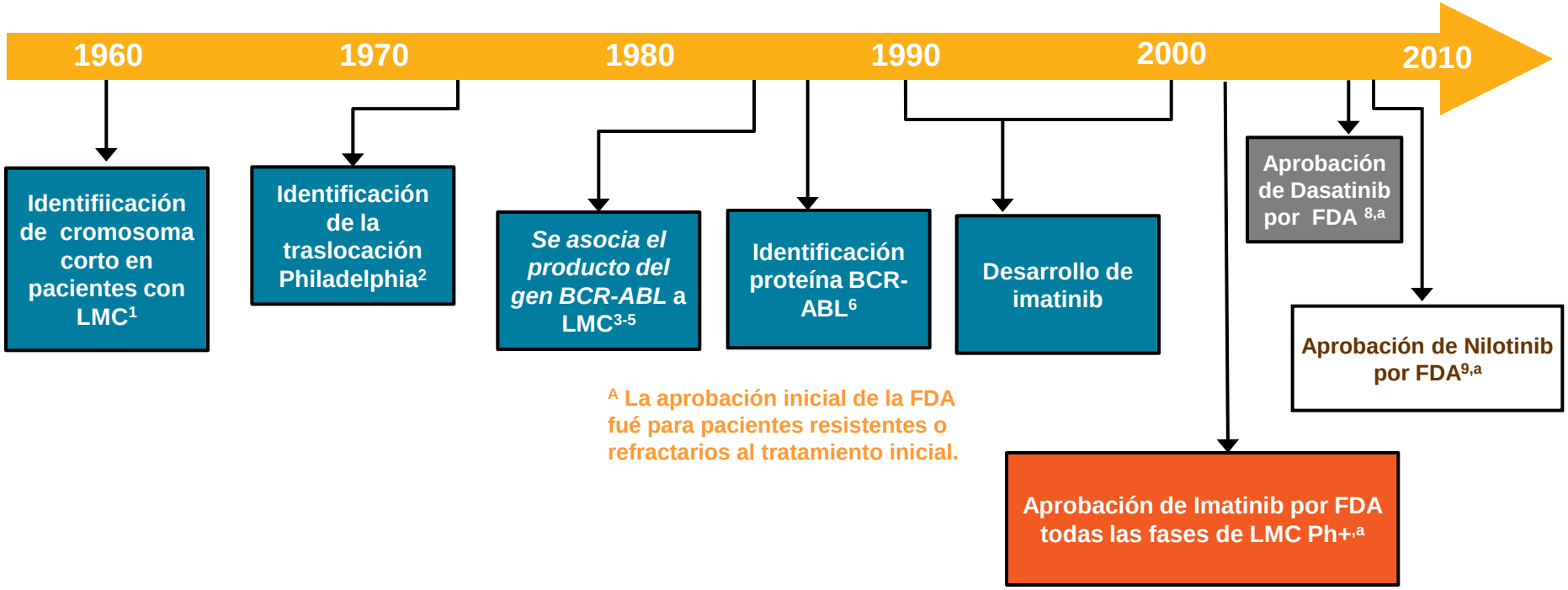
De vita VT & Rosenberg SA. Two hundred years of cancer research. NEJM 2012;366 (23):2207-14

Historia LMC y Imatinib

Best available approved treatment

Few options available prior to 1960

Busulfan **Hydroxyurea** **AlloSCT** **Interferon-alpha** **Inh tirosin cinasa**



[A] La aprobación inicial de la FDA fué para pacientes resistentes o refractarios al tratamiento inicial.

1. Nowell PC, Hungerford DA. *Science.* 1960;132:1497.
2. Rowley JD. *Nature.* 1973;243:290-293.
3. Bartram CR, et al. *Nature.* 1983;306(5940):277-280.
4. Heisterkamp N, et al. *Nature.* 1983;306(5940):239-242.
5. Groffen J, et al. *Cell.* 1984;36(1):93-99.
6. Ben-Neriah Y, et al. *Science.* 1986;233(4760):212-214.
7. Gleevec (imatinib) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2011.
8. Sprycel (dasatinib) [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2011.
9. Tasigna (nilotinib) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2011.

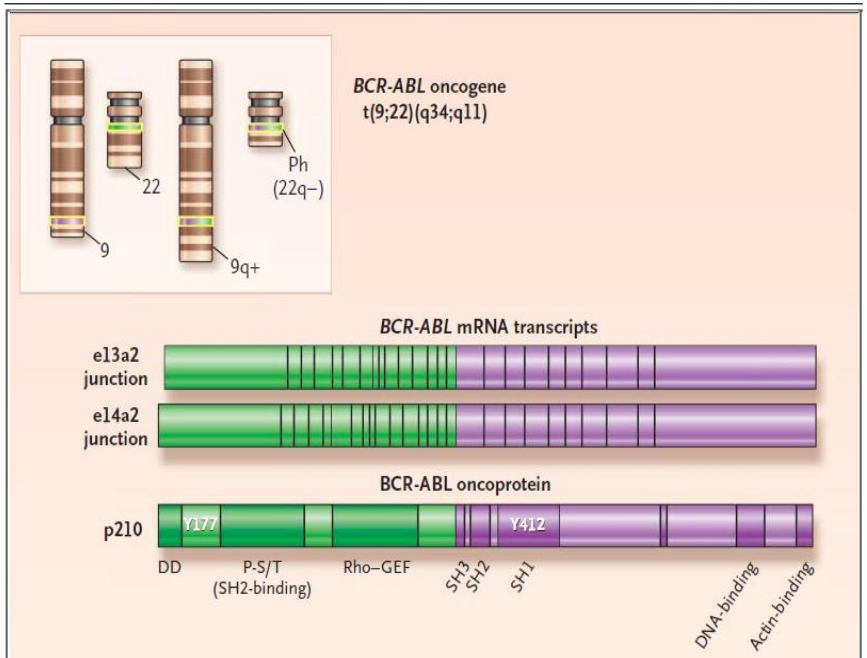


Figure 1. The t(9;22) Translocation and Its Products: the *BCR-ABL* Oncogene on the Ph Chromosome and the Reciprocal *ABL-BCR* on the Derivative 9q+ Chromosome.

In classic CML, *BCR-ABL* is transcribed into messenger RNA (mRNA) molecules with e13a2 or e14a2 junctions, which are then translated into the $p210^{BCR\text{-}ABL}$ oncoprotein. This oncoprotein is a hybrid containing functional domains from the N-terminal end of BCR (dimerization [DD], SRC-homology 2 [SH2]–binding, and the Rho GTP–GDP exchange-factor [GEF] domains) and the C-terminal end of ABL. (Only SRC-homology regions 2, 3, and 1 [SH2, SH3, and SH1, respectively], and the DNA- and actin-binding domains are shown.) Tyrosine 177 (Y177) in the BCR portion of the fusion gene and tyrosine 412 (Y412) in the ABL portion are important for the docking of adapter proteins and for BCR-ABL autophosphorylation, respectively. P-S/T denotes phosphoserine and phosphothreonine.

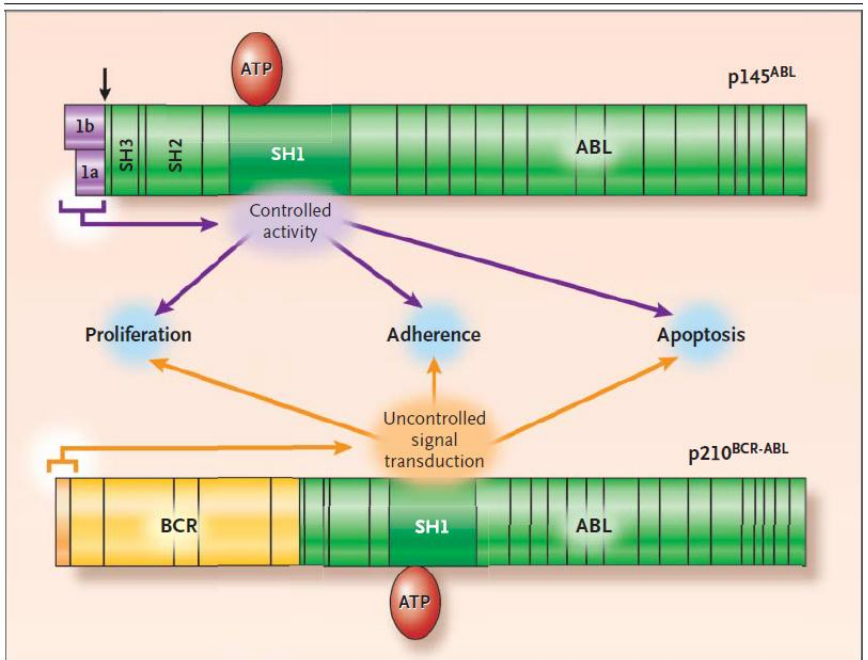


Figure 2. Physiologic Regulation by the Normal ABL Protein and Deregulation by BCR-ABL of Key Cellular Processes Such as Proliferation, Adherence, and Apoptosis.

The enzymatic (tyrosine kinase) activity of the normal ABL protein ($p145^{ABL}$), encoded by its SRC-homology 1 (SH1) domain, is kept under tight control, probably by the intramolecular binding of an N-terminal cap region encompassed by the first exon (1b or 1a) and the first part of exon a2.[53] In the BCR-ABL fusion protein ($p210^{BCR\text{-}ABL}$), lack of the ABL cap region and a dimerization domain encoded by the first exon of BCR are responsible for constitutive activation of the ABL SH1 domain, resulting in uncontrolled signal transduction and an abnormal cellular phenotype. The various functional domains of the ABL protein include the SRC-homology 3 and 2 regulatory domains (SH3 and SH2, respectively), the SH1 domain with its ATP-binding site, the nuclear-localization signal motif, the nuclear-export signal motif, the DNA-binding domain, and the G-actin and F-actin DNA-binding domains. The last two are important for the control of cytoskeletal organization, cell adherence, cell motility, and integrin receptor–mediated signal transduction.[54,55]

Goldman JM & Melo JV. Chronic Myeloid leukemia – advances in biology and new approaches to treatment. NEJM 2003;349:1451-64

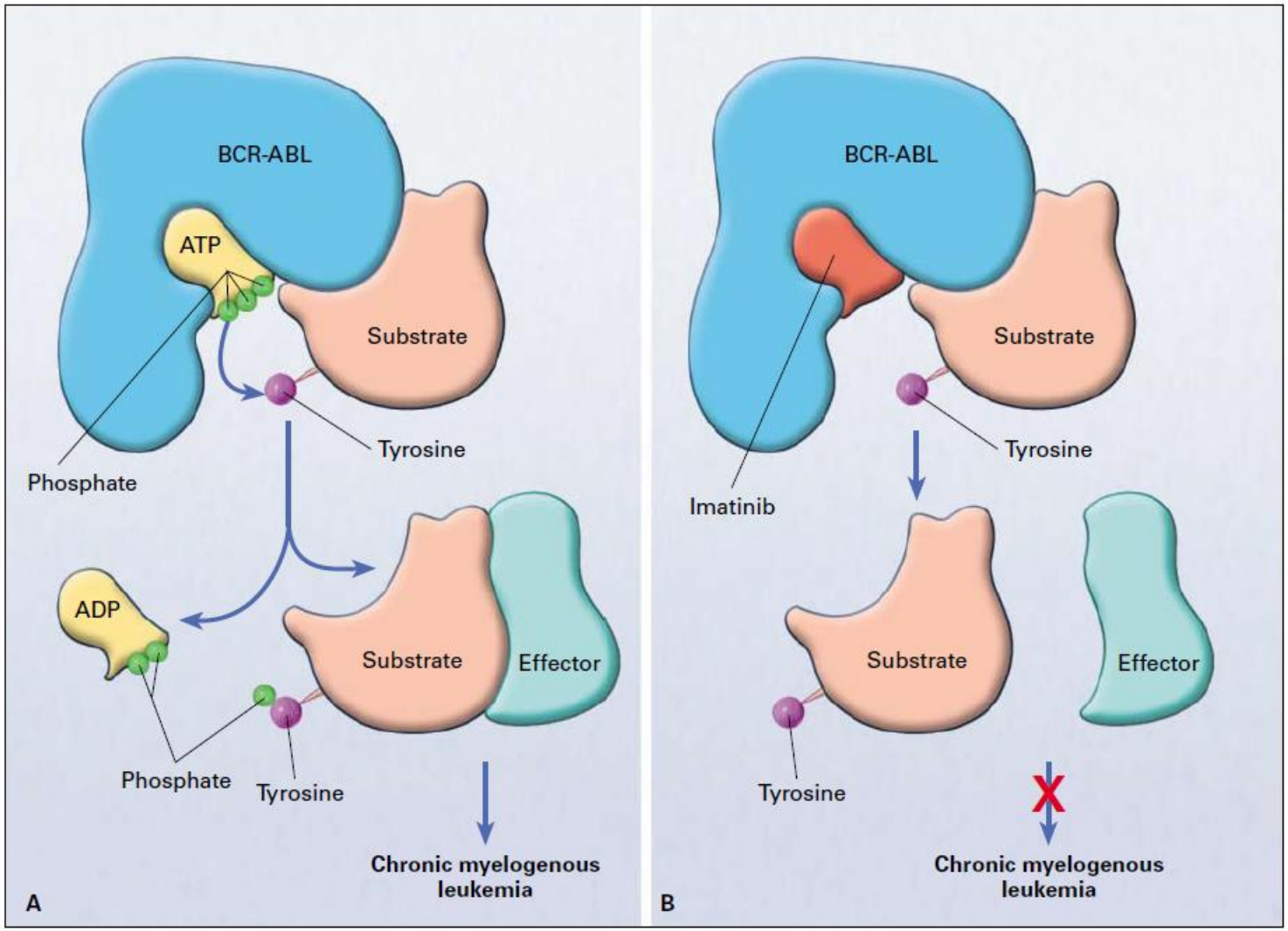


Figure 2. Mechanism of Action of BCR-ABL and of Its Inhibition by Imatinib.

Panel A shows the BCR-ABL oncoprotein with a molecule of adenosine triphosphate (ATP) in the kinase pocket. The substrate is activated by the phosphorylation of one of its tyrosine residues. It can then activate other downstream effector molecules. When imatinib occupies the kinase pocket (Panel B), the action of BCR-ABL is inhibited, preventing phosphorylation of its substrate. ADP denotes adenosine diphosphate. Adapted from Goldman and Melo[1] with the permission of the publisher.

Savage DG & Antman KH . Imatinib mesylate – a new oral targeted therapy . NEJM 2002;346:683-693

RECEPTORES TIROSIN-KINASA

Hospital de la Santa Creu i Sant Pau

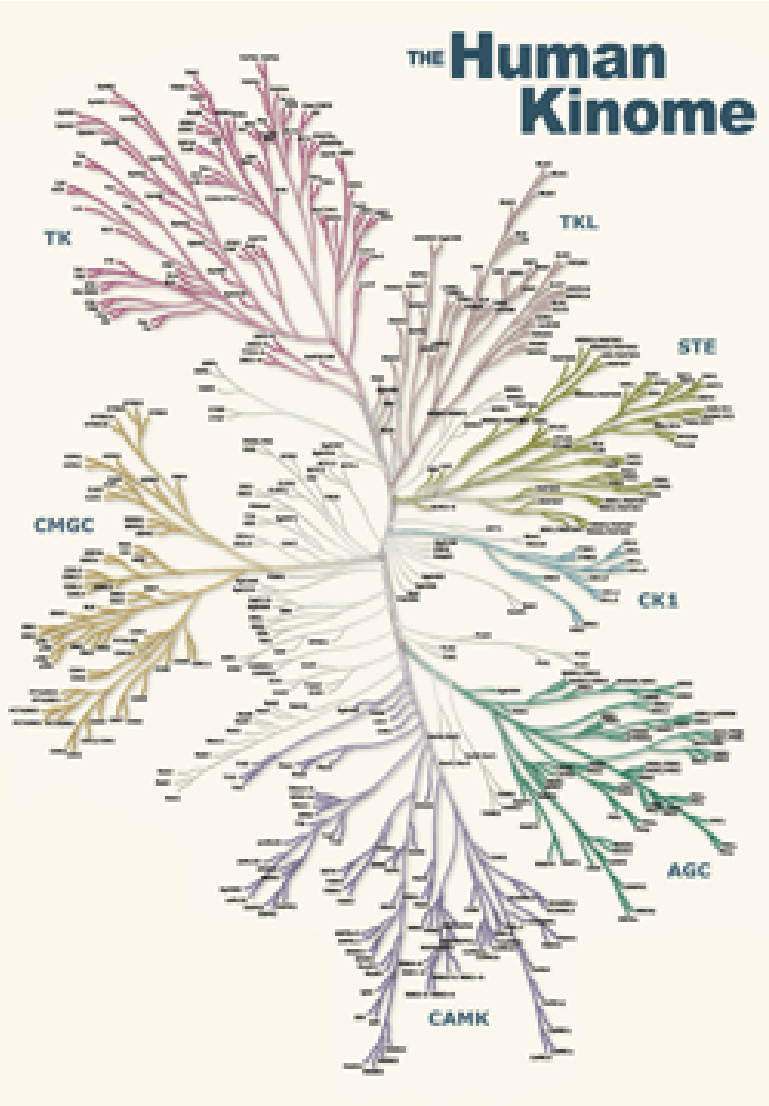
Tirosin-Kinasas

518 protein-Kinasas en el genoma humanos

- 90 genes tirosin-Kinasas

Son enzimas que catalizan la transferencia de fosfato de ATP a los residuos de tirosina en los polipéptidos que participan en las vías de señalización celular.

- Papel principal en señales intracelulares
- Implicadas en el crecimiento del tumor



Manning G, et al. Science 2002;298:1912

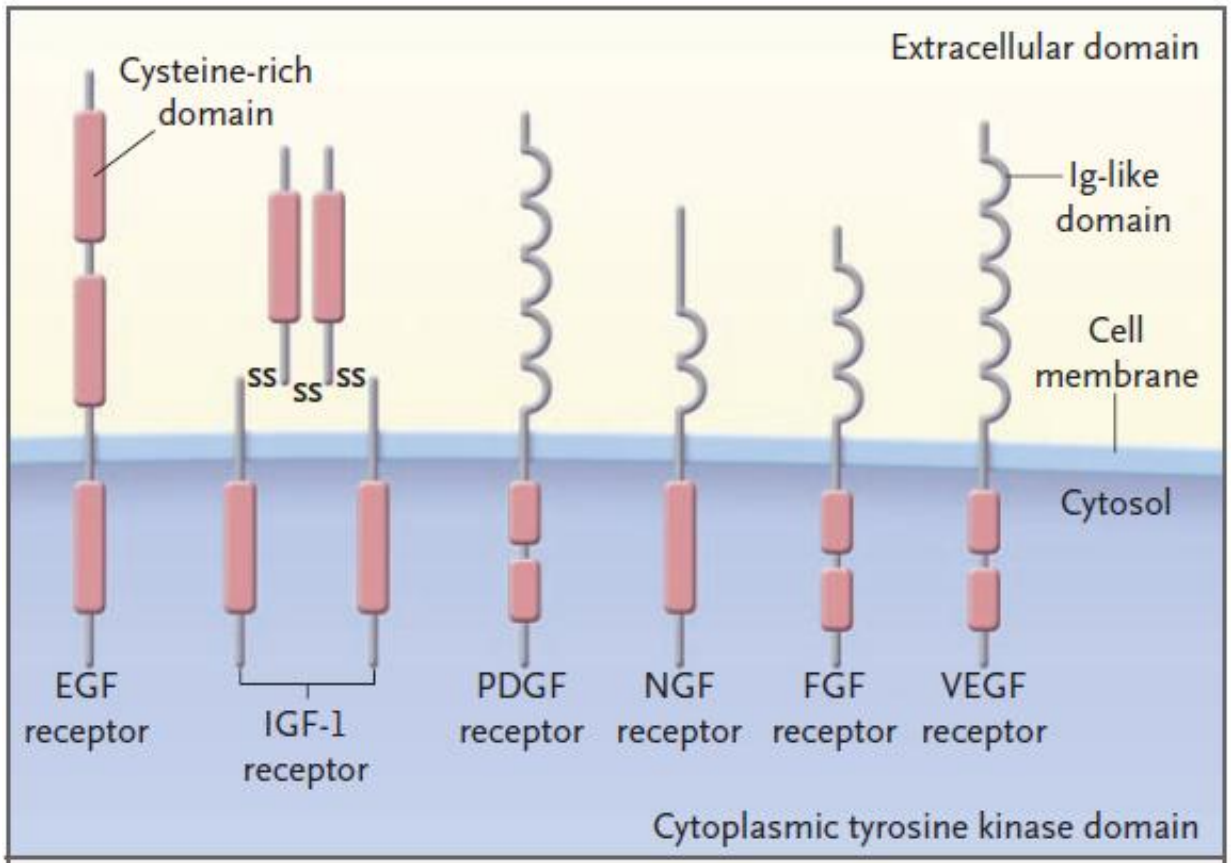


Figure 2. Examples of Receptor Tyrosine Kinases.

The epidermal growth factor (EGF), insulin-like growth factor 1 (IGF-1), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF) receptors have been found to be involved in a variety of human cancers. NGF denotes nerve growth factor, SS disulfide bonds, and VEGF vascular endothelial growth factor.

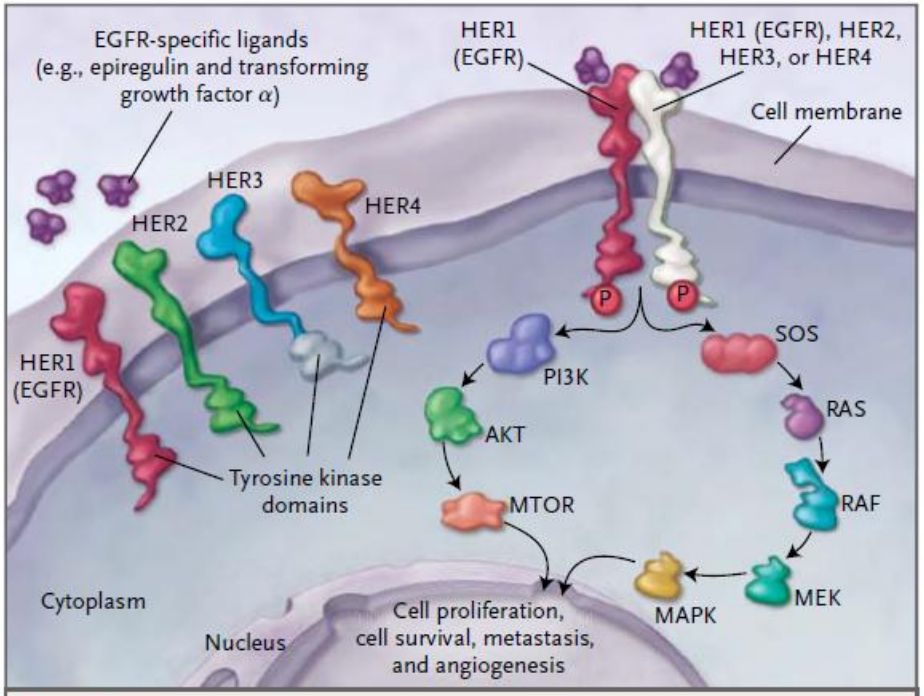


Figure 1. Epidermal Growth Factor Receptor (EGFR) Signaling Pathways.

Shown in the left portion of the figure are the four members of the ERBB (or HER) family of receptors. All four members of this family have tyrosine kinase domains in the cytoplasmic portion of the receptor. However, the tyrosine kinase domain of HER3 does not have catalytic activity. The right portion of the figure shows that binding of ligands to the HER family of receptors induces either homodimerization or heterodimerization of the receptors. Dimerization results in phosphorylation of the tyrosine residues of the EGFR kinase domain. The activated receptor may then phosphorylate a wide array of intracellular signaling cascades, such as the RAS–RAF–MEK–ERK and PI3K–AKT pathways, that induce cellular proliferation, angiogenesis, and metastases. EGFR amplification can obviate the requirement for ligand-induced dimerization. MTOR denotes mammalian target of rapamycin, P phosphorylation, and SOS son of sevenless.

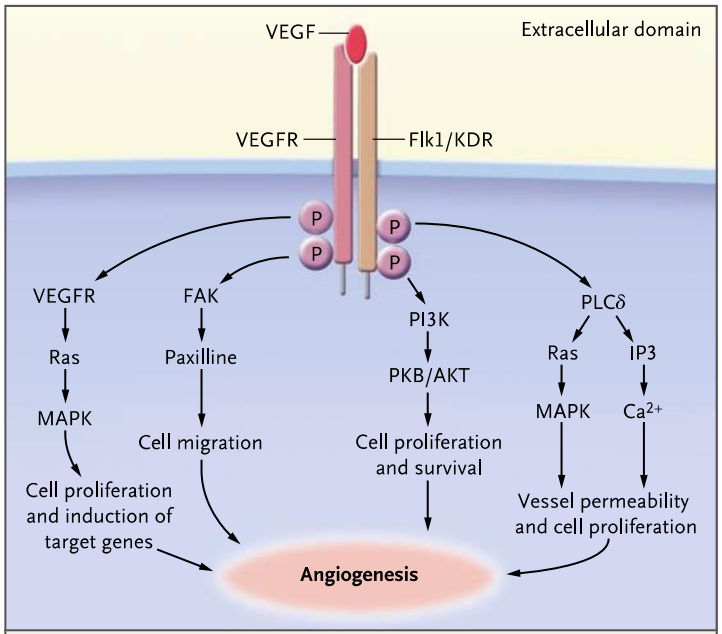


Figure 3. Role of VEGF–VEGFR Interaction in Angiogenesis.

Several pathways are activated by the interaction of vascular endothelial growth factor (VEGF) and VEGF receptors (VEGFR). FAK denotes fatal adhesion kinase, Flk fetal liver kinase, IP3 inositol triphosphate, KDR kinase-insert domain–containing receptor, MAPK mitogen-activated protein kinase, PI3K phosphoinositol 3-kinase, PKB protein kinase B, and PLC phospholipase C.

Cataldo VD, et al. Treatment of non-small-cell lung cancer with erlotinib or gefitinib. NEJM 2011;364:947-955
Croce CM. Oncogenes and cancer. NEJM 2008;358:502-11

Table 1. Cancer Therapies That Target Oncogenic Proteins.*

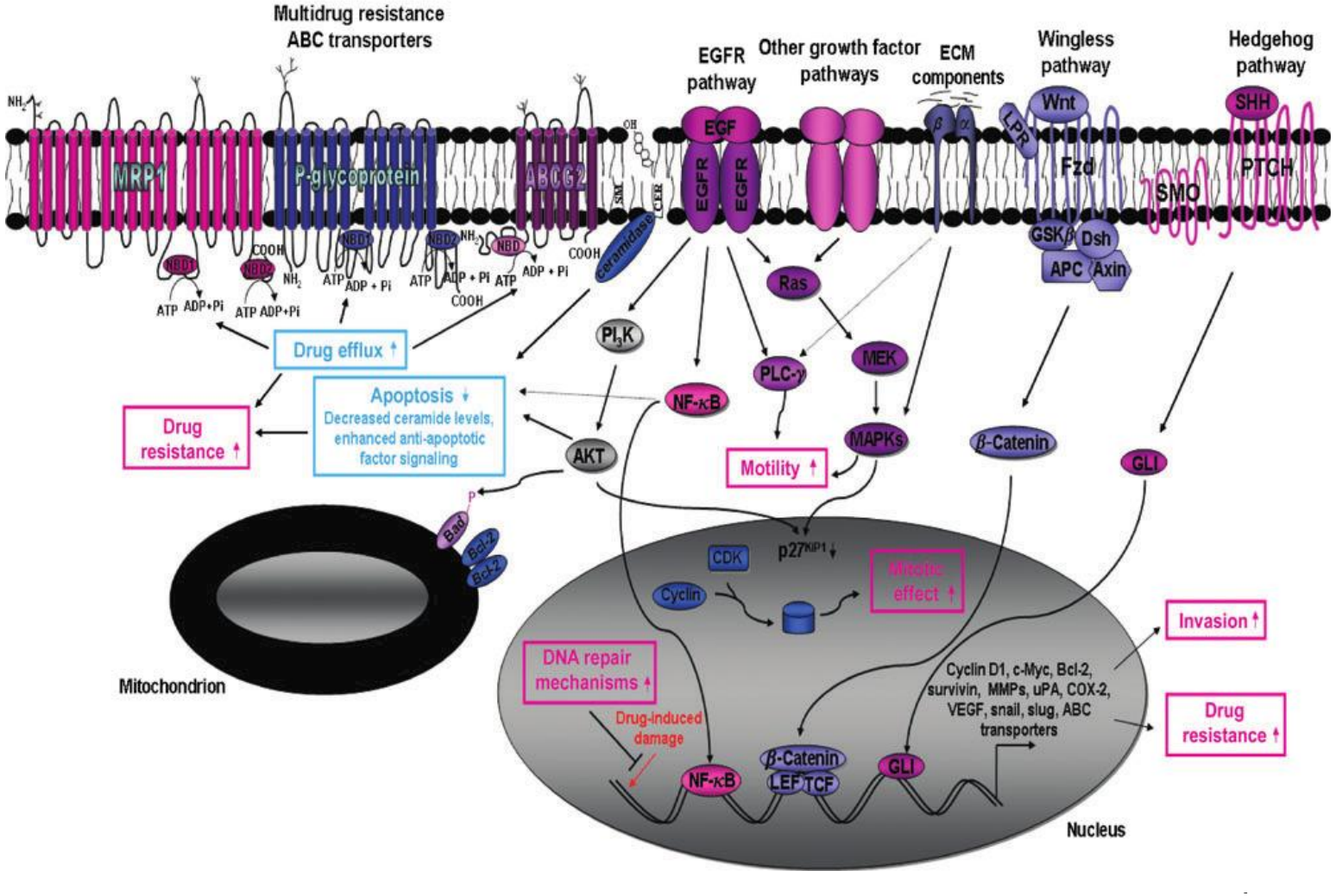
Anticancer Drug	Target	Disease
Monoclonal antibodies		
Trastuzumab (Herceptin, Genentech)	ERBB2	Breast cancer
Cetuximab (Erbitux, ImClone)	EGFR	Colorectal cancer
Bevacizumab (Avastin, Genentech)	VEGF	Colorectal cancer, non–small-cell lung cancer
Small molecules		
Imatinib (Gleevec, Novartis)	ABL, PDGFR, KIT	Chronic myelogenous leukemia, gastrointestinal stromal tumors, chordoma
Gefitinib (Iressa, AstraZeneca)	EGFR	Non–small-cell lung cancer
Erlotinib (Tarceva, Genentech)	EGFR	Non–small-cell lung cancer
Sorafenib (Nexavar, Bayer/Onyx)	VEGFR, PDGFR, FLT3	Renal-cell carcinoma
Sunitinib (Sutent, Pfizer)	VEGFR, PDGFR, FLT3	Gastrointestinal stromal tumors, renal-cell carcinoma

* EGFR denotes epidermal growth factor receptor, FLT3 FMS-like tyrosine kinase 3, PDGFR platelet-derived growth factor receptor, and VEGF vascular endothelial growth factor.

Croce CM. Oncogenes and cancer. NEJM 2008;358:502-11

RESISTENCIAS

Molecular mechanisms involved in sustained growth, survival and drug-resistance of cancer cells



Mimeault M, et al. Recent advances on the molecular mechanisms involved in the drug resistance of cancer cells and novel targeting therapies. Clinical Pharmacology and therapeutics 2008;83:673-691

Table 5 Resistance mechanism to tyrosine kinase inhibitors

	Mechanism	Target/drug/disease	Ref.
1	(Secondary) mutation of the tyrosine kinase	Bcr-Abl in CML, FLT3 in AML, EGFR in NSCLC, c-KIT in GIST	[12]
2	Gene amplification and subsequent overexpression of the protein kinase	Bcr-Abl in CML + c-KIT in GIST	[12]
3a	Activation of other signaling pathways	PDGFR mutation in c-KIT mutated GIST, MET overexpression in EGFR mutated NSCLC	[50]
3b	Overexpression of kinases downstream of the kinase	LYN in CML	
4	Lower intracellular drug concentrations because of:		
4a	Extracellular sequestration of the inhibitor by binding to α acid glycoprotein	PKC412, imatinib	[99]
4b	Decreased expression or activity of drug influx pumps	OCT1, imatinib	[52]
4c	Increased expression or activity of drug efflux pumps	BCRP, P-glycoprotein (imatinib)	[51,60]

NSCLC: Non small cell lung cancer; PDGFR: Platelet derived growth factor receptor; EGFR: Epidermal growth factor receptor; CML: Chronic myeloid leukemia; GIST: Gastrointestinal stromal tumors; AML: Acute myeloid leukaemia.

Genetic modifications:
Point Mutations (Activating mutations).
Amplifications (Target gene).
Deletions.
Protein Modifications:
Overexpression of the target protein.
Activation of alternative pathways.
Overexpression of Multidrug resistance genes.

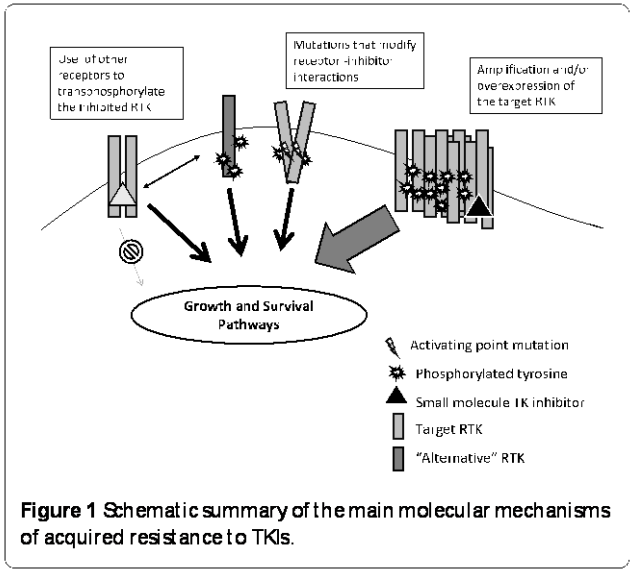


Figure 1 Schematic summary of the main molecular mechanisms of acquired resistance to TKIs.

Broekman F, et al. Tyrosine kinase inhibitors: multi-targetedor single-targeted? World J Clin Oncol 2011;2(2):80-93
Sierra JR, et al. Molecular mechanisms of acquired resistance to tyrosine kinase targeted therapy. Molecular cancer 2010;9

Pero no todo son malas noticias…

ENTINOSTAT:

Es un inhibidor de histona deacetilasa que ha demostrado vencer la resistencia de los inhibidores tirosin kinasa del receptor de factor de crecimiento epidérmico en un estudio llevado a cabo en pacientes con cáncer de pulmón tratados con erlotinib

FÁRMACOS

Inhibidores tirosin-kinasa

Específicos

Indicaciones más limitadas

Menos efectos adversos

Poco frecuente

ERLOTINIB

MultiKinasa

Teoricamente el objetivo son varias vías

Puede actuar en varios tumores diferentes

Posiblemente más tóxicos

SORAFENIB

Inh VEGF
Sunitinib
Sorafenib
Pazopanib
Axitinib
Tivozanib
Vandetanib
Cediranib
Semaxinib
Vatalanib
Foratinib
Motesanib
Cabozantinib
Cediranib
Regorafenib

Inh BCR-ABL
Imatinib
Dasatinib
Nilotinib
Bosutinib
Ponatinib
Bafetinib

Inh EGFR
Gefitinib
Erlotinib
Lapatinib
Vandetanib
Afatinib
Dacomitinib
Canertinib

Inh Kit
Imatinib
Sunitinib
Pazopanib
Masatinib
Semaxinib
Vatalanib
Motesanib
Regorafenib

Inh HER2
Lapatinib
Neratinib
Afatinib

Inh BRAF
Vemurafenib
Dabrafenib

Inh PDGFR
Imatinib
Sunitinib
Sorafenib
Pazopanib
Regorafenib
Masatinib
Motesanib
Vatalanib

Inh JAK2
Ruxolitinib

Inh FLT3
Sunitinib
Sorafenib
Quizartinib
Semaxinib

Inh MEK
Selumetinib

Inh RET
Vandetanib

Inh IGFR
AMG479

Inh MET
Trametinib
Cabozantinib

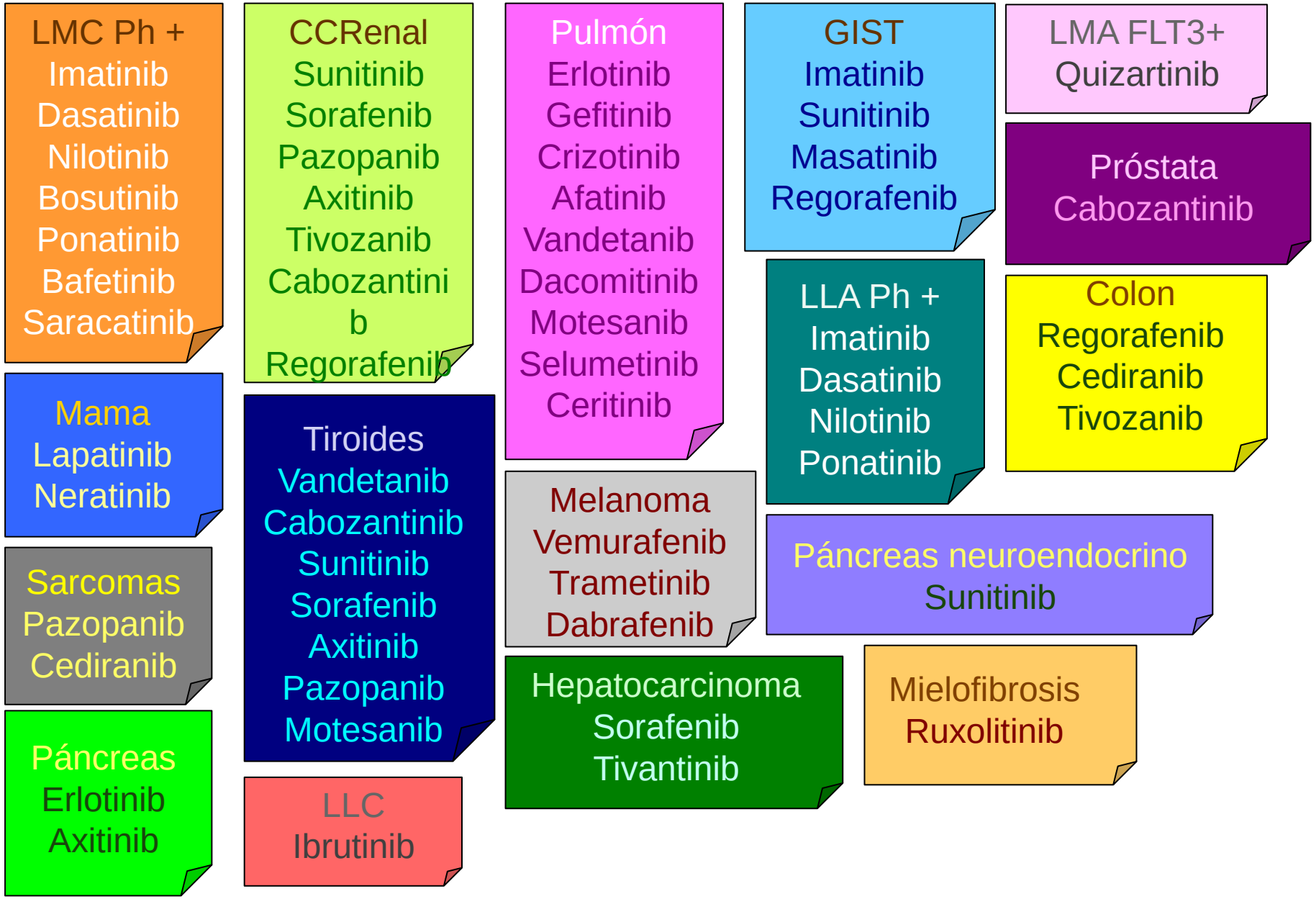
Inh ALK
Crizotinib
Ceritinib

Inh BTK
Ibrutinib

Inh cMet
Crizotinib
Foretinib
Tivantinib

FLT3 FMS like tironkinasa 3; BTK Brutom tironKinasa

Arora A& Scholar EM. Role of tyrosine kinase inhibitors in cancer therapy. JPET 2005;315:971-979


LMC Ph +
Imatinib
Dasatinib
Nilotinib
Bosutinib
Ponatinib
Bafetinib
Saracatinib
CCRenal
Sunitinib
Sorafenib
Pazopanib
Axitinib
Tivozanib
Cabozantinib
Regorafenib
Pulmón
Erlotinib
Gefitinib
Crizotinib
Afatinib
Vandetanib
Dacomitinib
Motesanib
Selumetinib
Ceritinib
GIST
Imatinib
Sunitinib
Masatinib
Regorafenib
LMA FLT3+
Quizartinib
Próstata
Cabozantinib
LLA Ph +
Imatinib
Dasatinib
Nilotinib
Ponatinib
Colon
Regorafenib
Cediranib
Tivozanib
Mama
Lapatinib
Neratinib
Tiroides
Vandetanib
Cabozantinib
Sunitinib
Sorafenib
Axitinib
Pazopanib
Motesanib
Melanoma
Vemurafenib
Trametinib
Dabrafenib
Páncreas neuroendocrino
Sunitinib
Sarcomas
Pazopanib
Cediranib
Hepatocarcinoma
Sorafenib
Tivantinib
Mielofibrosis
Ruxolitinib
Páncreas
Erlotinib
Axitinib
LLC
Ibrutinib

Características generales

- Moléculas pequeñas que se administran por vía oral → Adherencia
- Administrados en monoterapia o asociados a QT tradicional
- Efectos adversos diferentes a la QT tradicional
- Interacciones → Conciliación

Información individualizada al paciente

EFECTOS ADVERSOS

Efectos adversos

- Gastrointestinales
  - Diarrea
  - Náuseas y vómitos
- Reacciones cutáneas
  - Rash acneiforme
  - Síndrome mano-pie
  - Foliculitis
  - Alopecia
  - Cambios color piel/pelo
  - Alteraciones uñas
- Alteraciones hepáticas
- Cardiovasculares
  - Insuficiencia cardiaca
  - HTA
  - Prolongación QT
  - Retención de líquidos
- Efectos metabólicos
  - Hipotiroidismo
  - Hiperglucemia
  - Lipasa – pancreatitis
- Hematológicas
- Alteraciones coagulación
  - Aumento sangrado
  - Proteinuria

Los efectos adversos se relacionan con la eficacia del fármaco?

ELSEVIER

Urologic Oncology: Seminars and Original Investigations 30 (2012) 704–710

UROLOGIC ONCOLOGY

Original article

The impact of sunitinib-induced hypothyroidism on progression-free survival of metastatic renal cancer patients: A prospective single-center study

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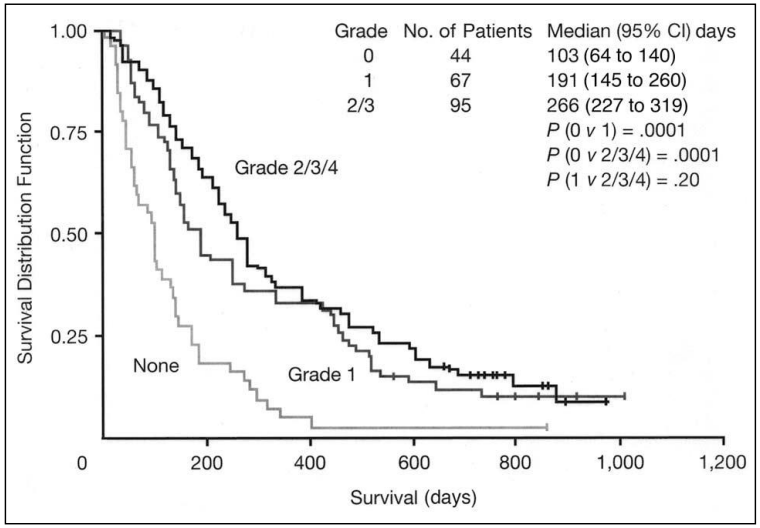


Fig 1. Kaplan-Meier curve showing survival by grade of rash: combined data from three phase II trials of erlotinib. Adapted with permission, Clark et al.[51]

Sbaldazzi et al. The impact of sunitinib-induced hypothyroidism on progression-free survival of metastatic renal cancer patients: a prospective single-center study. Seminars and original investigators 2012;30:704-710
Pérez Soler R, et al. Cutaneous adverse effects with HER1/EGFR-targeted agents: is there a silver lining? JCO 2005; 23:5235-5246

INFORMACIÓN AL PACIENTE

Hospital de la Santa Creu i Sant Pau

POSOLOGIA

IMATINIB se administra por **via oral**
La dosis recomendada es según prescripción médica

COMO se debe TOMAR Imatinib?

– Tomar con alimentos, preferentemente por la mañana.
– Evite el contacto con la piel. Lávese las manos antes y después de cada toma
– Los comprimidos deben tragarse enteros con un vaso de agua, sin masticar ni chupar.
– Si tiene problemas para tragar puede disolverlos en agua y tomarlos inmediatamente.
– Mantenga siempre el mismo horario.

.

QUE HACER SI...? :

– Si se ha olvidado de tomar una dosis: tómela lo antes posible. Si han transcurrido mas de 12 horas espere a la siguiente toma y no doble nunca la dosis.
– Si vomita no repita la dosis.
– En caso de duda coméntelo con su médico o farmacéutico.

Cuando NO debe tomar Imatinib?

– Si usted es alérgico a imatinib así como a cualquiera de los componentes del comprimido.
– Si está embarazada o en período de lactancia

PRECAUCIONES

– Si padece una enfermedad hepática.
– Si ha sufrido una enfermedad que afecte de manera importante la absorción intestinal o si se ha sometido a una resección quirúrgica de intestino o estómago.
– Adopte 2 medidas anticonceptivas si usted o su pareja puede quedarse embarazada y manténgalas hasta 2 semanas después de haber finalizado el tratamiento.
– Consulte con su médico o farmacéutico antes de vacunarse.
– Se recomienda usar gel de baño sin detergente, cremas hidratantes de avena o aloe vera y champú suave.
– Protéjase del sol con ropa adecuada y crema con filtro solar de protección superior a 15.

INTERACCIONES

Pregunte a su médico o farmacéutico antes de tomar un medicamento, vitamina o planta medicinal, especialmente si toma tratamiento para:
– Antifúngicos (para tratar infecciones por hongos): ketoconazol, itraconazol, voriconazol.
– Antibióticos: eritromicina, claritomicina, rifampicina, telitromicina, .
– Antivirales: atazanavir, indinavir, nefazodona, nelfinavir, ritonavir, saquinavir.
– Antiepilépticos : fenobarbital. carbamazepina, fenitoína
– Anticoagulantes: warfarina, acenocumarol
– Corticoides: dexametasona
– Otros: paracetamol, levotiorixina, simvastatina
– Hierba de San Juan o hipérico
– Zumo de pomelo.

EFECTOS ADVERSOS:

Los efectos adversos mas frecuentes, que no significa que aparezcan en todos los pacientes, son:
– Dolor de cabeza
– Vómitos, náuseas
– Diarrea, estreñimiento
– Indigestión
– Erupciones cutáneas
– Inflamación de los tobillos, cara.
– Disminución del apetito.
– Cansancio
– Dolor de las articulaciones
– Calambres musculares

Comente a su médico o farmacéutico si presenta alguno de estos efectos adversos o cualquier otro que crea que puede estar relacionado con la medicación.

Avise rápidamente a su médico si tiene:
– Una reacción alérgica grave: (enrojecimiento de la piel, dificultad al respirar...).
– Signos de infección como tos, escalofríos, fiebre > 38ºC, dificultad al orinar.
– Signos de sangrado como heces negras, sangre en la orina o hematomas importantes.
– Aumento rápido de peso
– Dificultad para respirar
– En caso de sobredosis.

CONSERVACIÓN

Mantenga los comprimidos en su envase original, a temperatura ambiente, protegidos de la luz y de la humedad.

CADUCIDAD

No utilizar después de la fecha de caducidad indicada en el envase.

ADVERTENCIAS

Mantenga los medicamentos fuera del alcance de los niños.

Este medicamento sólo puede conseguirse a través del Servicio de Farmacia del Hospital, con la receta que le hará su médico de este Centro

Devuelva la medicación sobrante a la Farmacia del Hospital

Las mujeres embarazadas deberán tener especial cuidado en evitar el contacto con el contenido de los comprimidos.

RECOMENDACIONES AL PACIENTE

DIAS	Nº COMPRIMIDOS		Frecuencia
	100mg	400mg	

Notas:

Este tríptico NO contiene toda la información de este fármaco y sólo pretende ser un resumen para ayudar al paciente con su tratamiento.

Si tiene cualquier duda o precisa más información contacte con su médico o farmacéutico.

COMO CONTACTAR

Teléfono Farmacia

Horario

Logo Hospital

INFORMACIÓN DE MEDICAMENTOS

IMATINIB

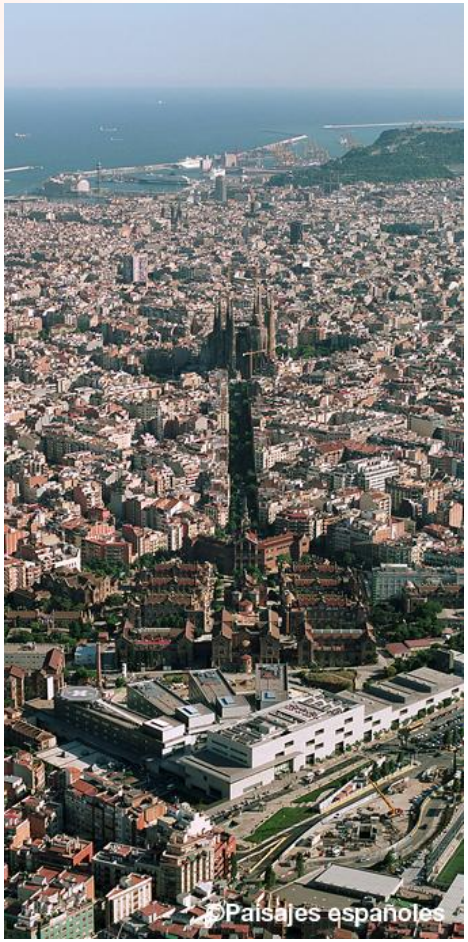
Glivec®

Comprimidos 400 y 100 mg

Nombre paciente:

Fecha:

¡Muchas Gracias!



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