Corso di Laurea in Infermieristica – sedi di Firenze e Pistoia

Modulo di oncologia medica

Lezioni dell'AA 2017-2018

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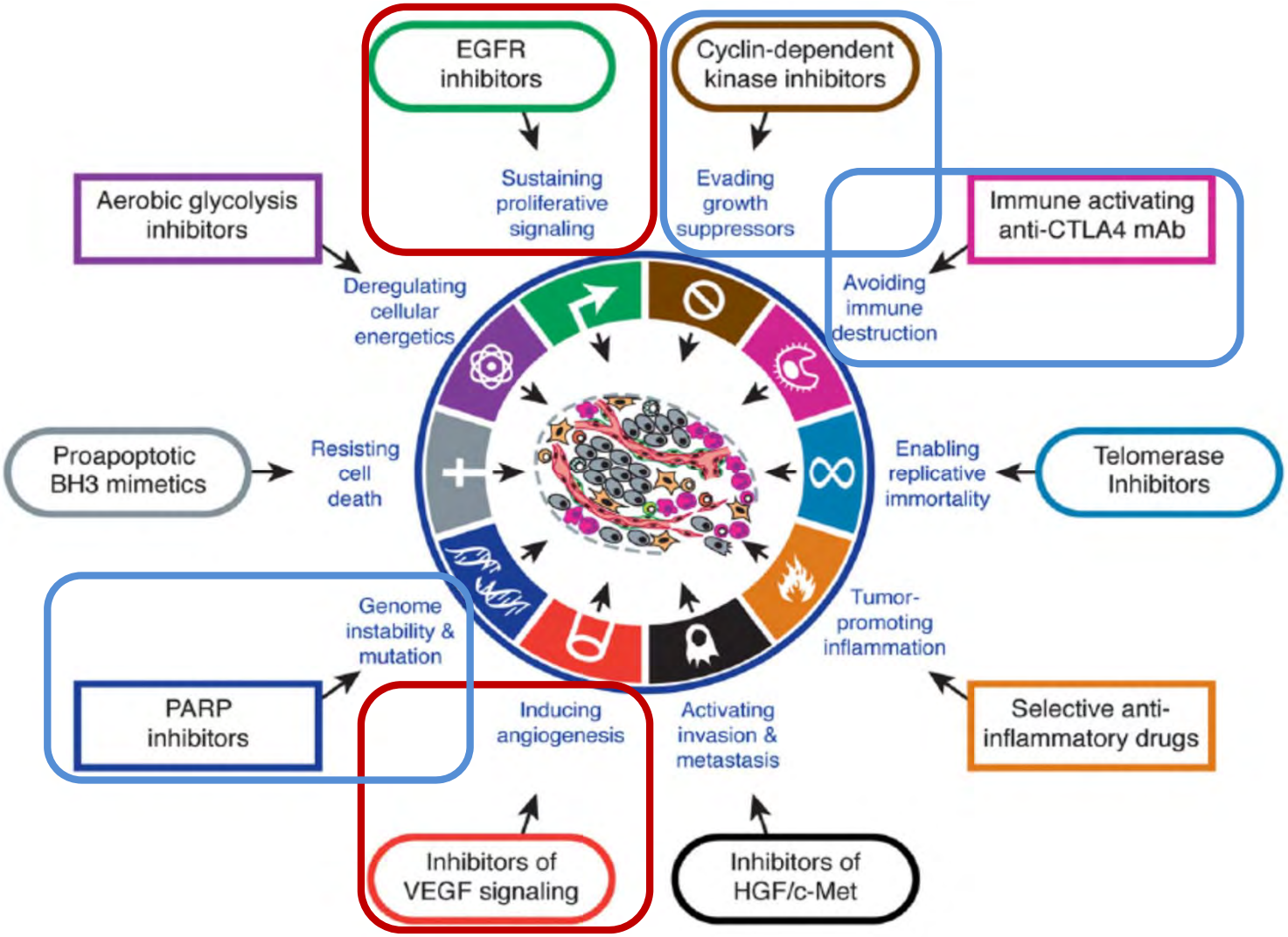
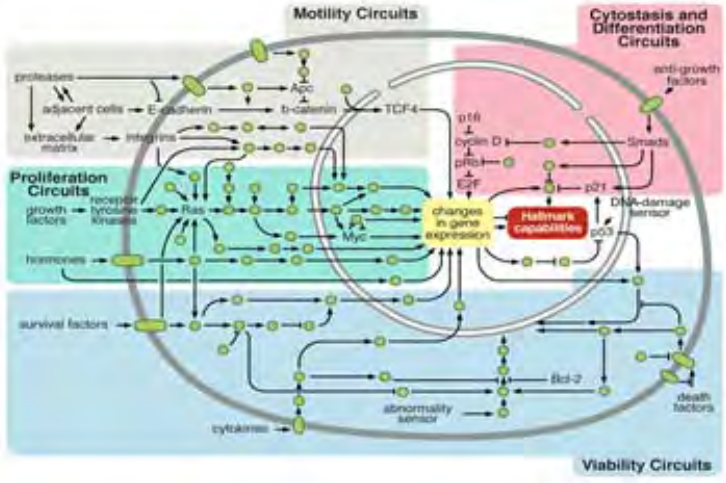
Chemioterapia bersaglio-specifica

Therapeutic targeting of the hallmarks of cancer



Hanahan D & and Weinberg RA, Cell, 2011

Signal transduction pathways involved in the proliferation and survival of cancer cells

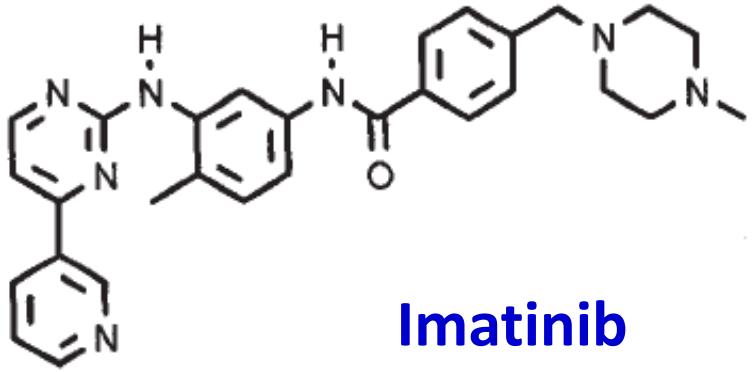


Hanahan & Weinberg Cell 2011

Tipi di terapia medica in oncologia (II)
Chemioterapia bersaglio-specifica (terapia molecolare, targeted therapy)

- **Farmaci diretti contro "bersagli molecolari" specifici della cellula neoplastica o delle cellule del microambiente tumorale (vasi, stroma, sistema immunitario):**
  - **inibitori di proteine coinvolte nella trasduzione del segnale (anticorpi monoclonali, composti chimici)**

Major classes of cancer therapeutics – 2. Protein kinase inhibitors



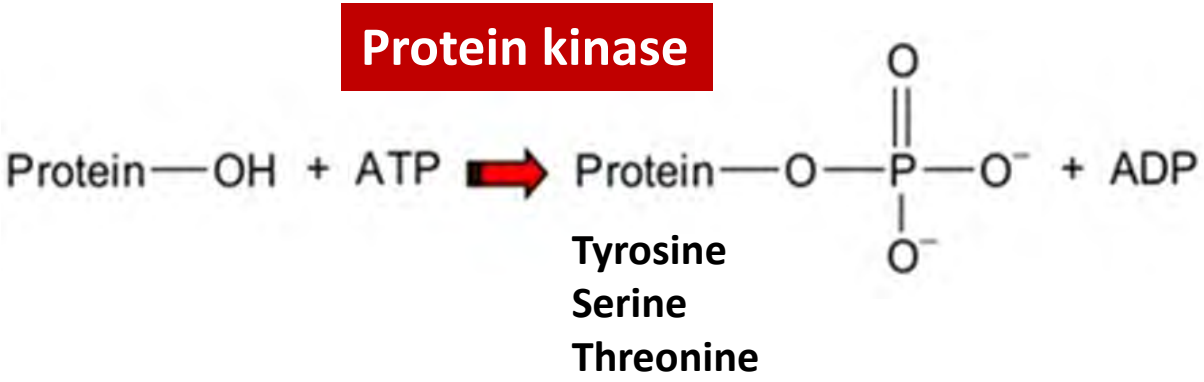
Imatinib

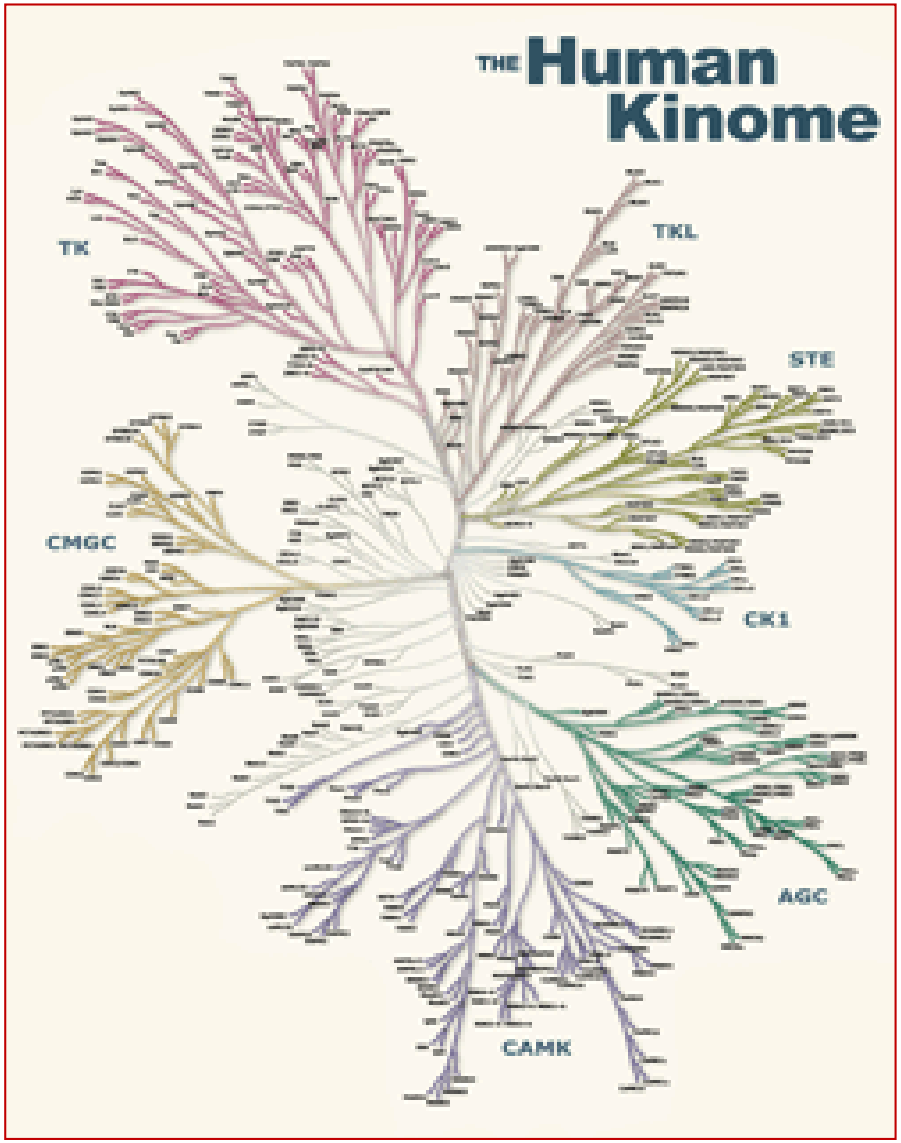
Molecularly directed development
Discovery based on receptors
Intracellular action
Cytostatic effect (reversible or irreversible)
Selective (less toxic)
Continuous administration (following Minimum Effective Dose)
~ 0.5–1.5 kDa MW
Orally available

From Jimeno A et al. Curr Cancer Ther Rev, 2005 modified

Protein kinases: major targets for novel agents

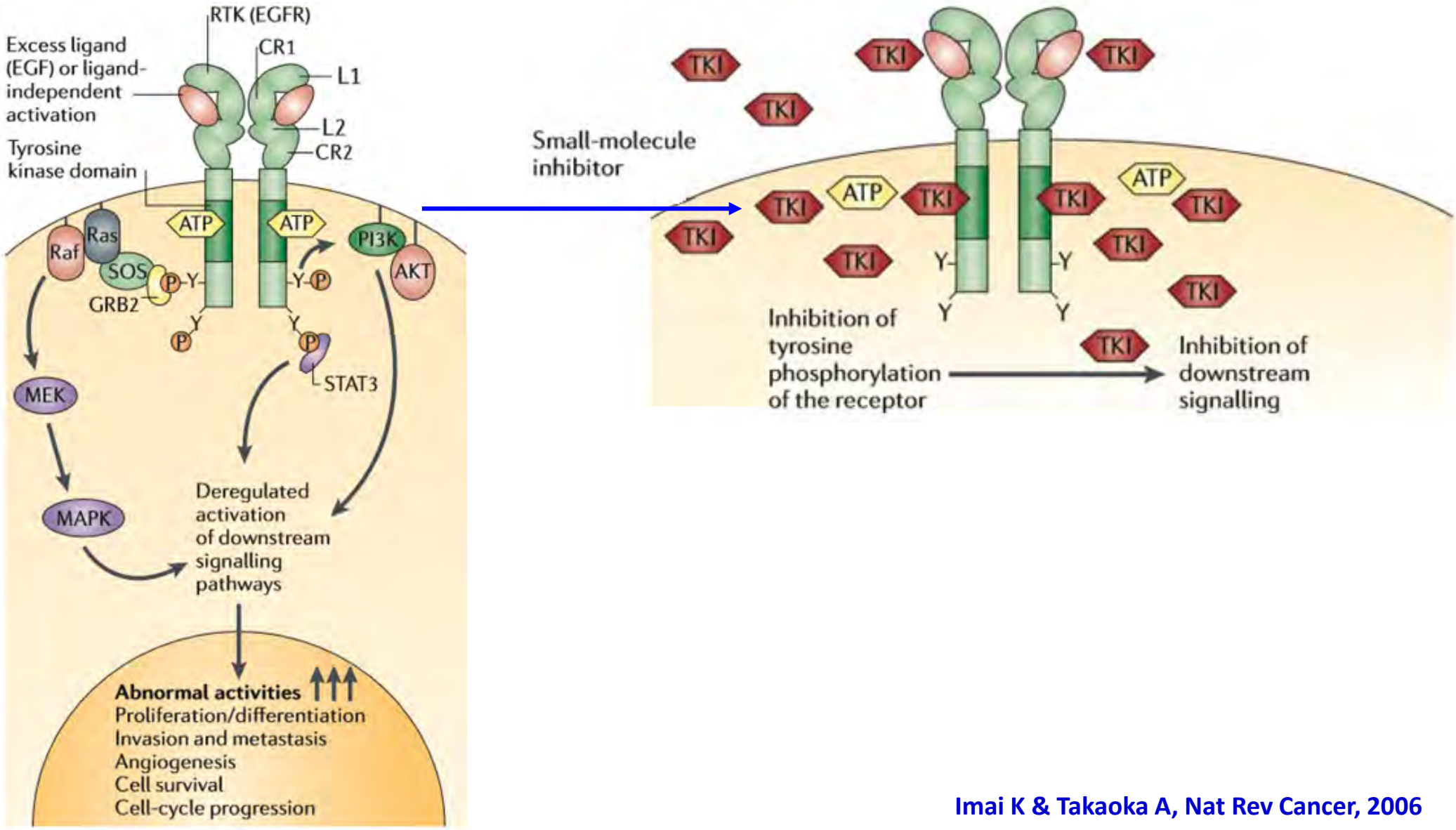
- There are 518 protein kinases in the human genome (90 tyrosine kinases)
- Major role in intracellular signalling
- Deregulation of kinase activity implicated in the growth and survival of many solid tumour types
- Protein kinases catalyze the transfer of the terminal phosphate of ATP (or GTP) to protein substrates





Manning G et al. Science, 2002

Mechanism of small-molecule inhibitors for targeting RTKs in cancer cells

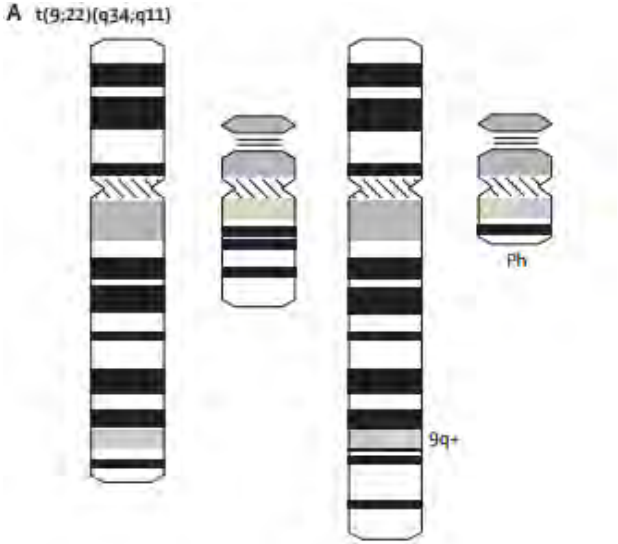


Imai K & Takaoka A, Nat Rev Cancer, 2006

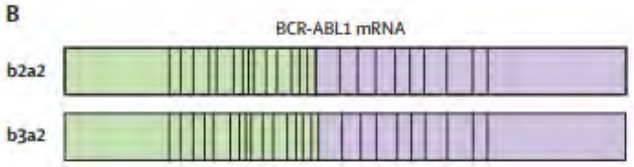
Chronic myeloid leukaemia

Pathogenesis

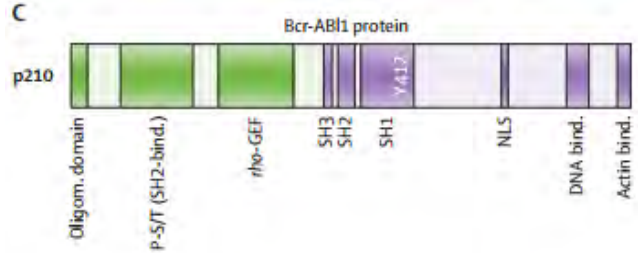
The t(9;22) reciprocal translocation (A) results in the creation of the BCR-ABL1 fusion gene



which is in turn transcribed to a BCR-ABL1 mRNA (B)



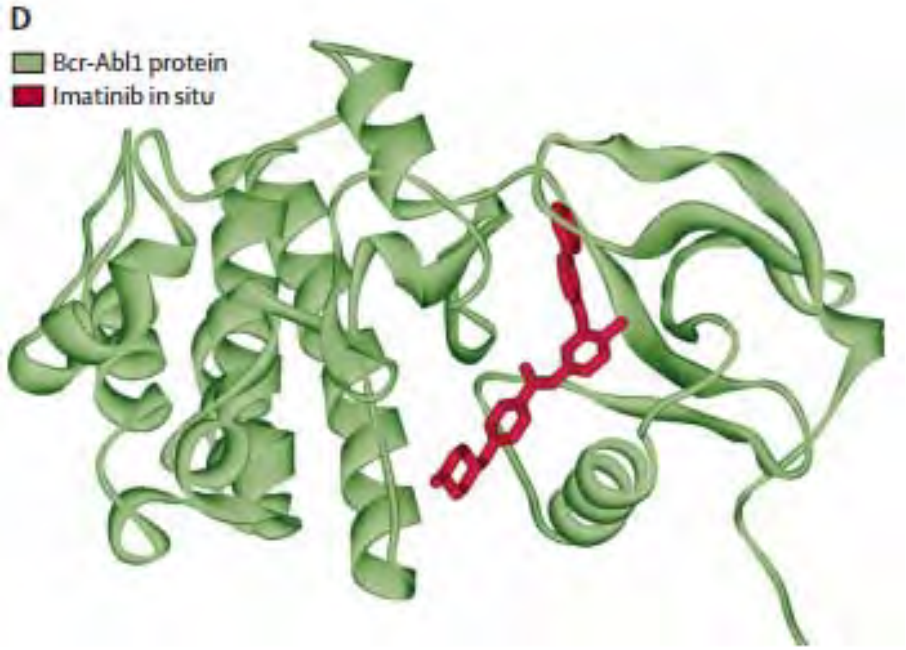
and translated to the Bcr-Abl protein (C)



Epidemiology

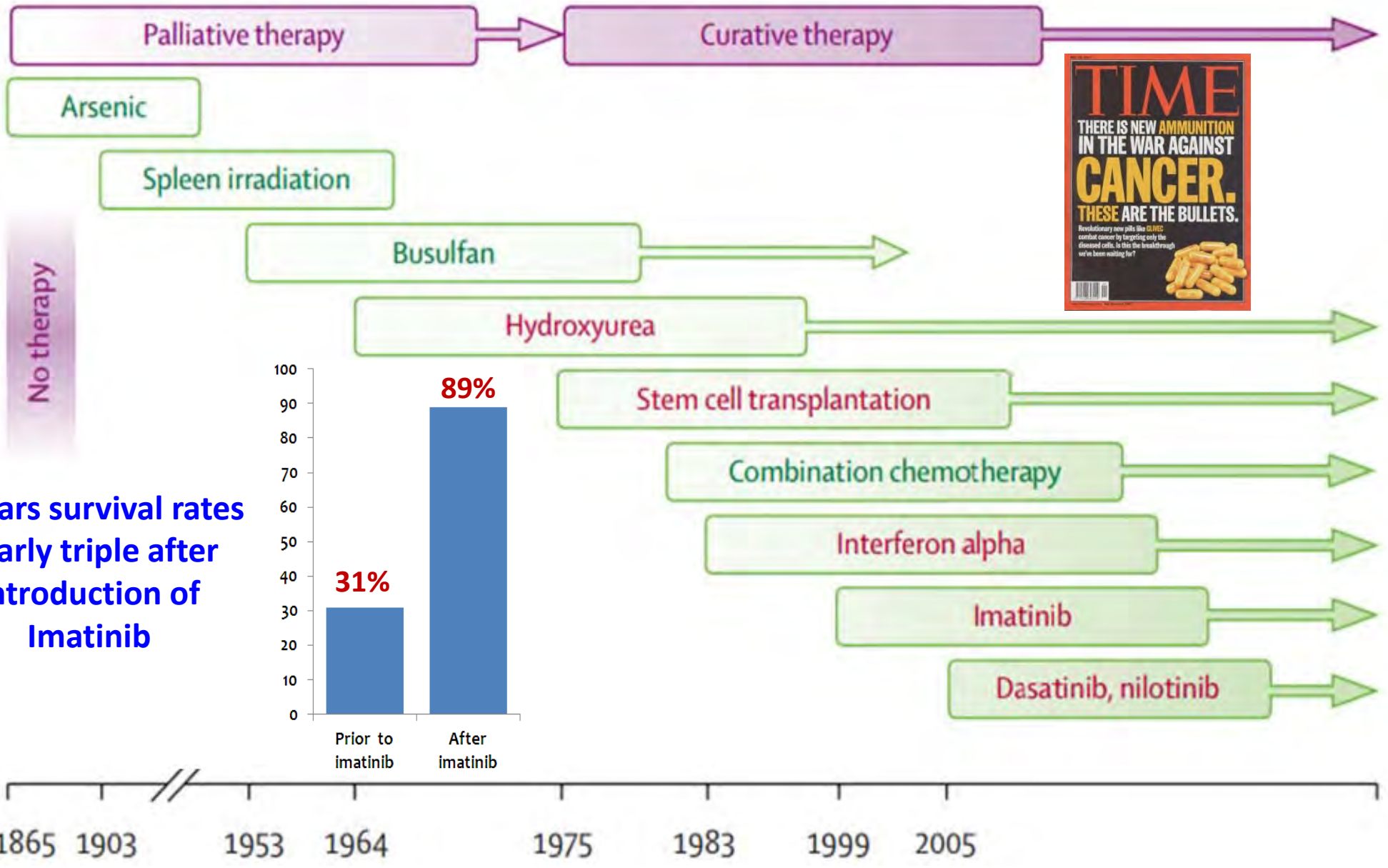
Chronic myeloid leukaemia affects about one individual per 100 000 population per year, and accounts for 15% of all new cases of leukaemia in the Western hemisphere.

Interaction of BCR-ABL1 protein with imatinib in ATP binding loop (D)



Apperley JF. Lancet, 2015

Development of treatments for CML



5-years survival rates nearly triple after introduction of Imatinib

The arrows show the use of treatments over time. Treatments in red indicate commonly used treatments for chronic phase CML.

Hehlmann R et al., Lancet, 2007

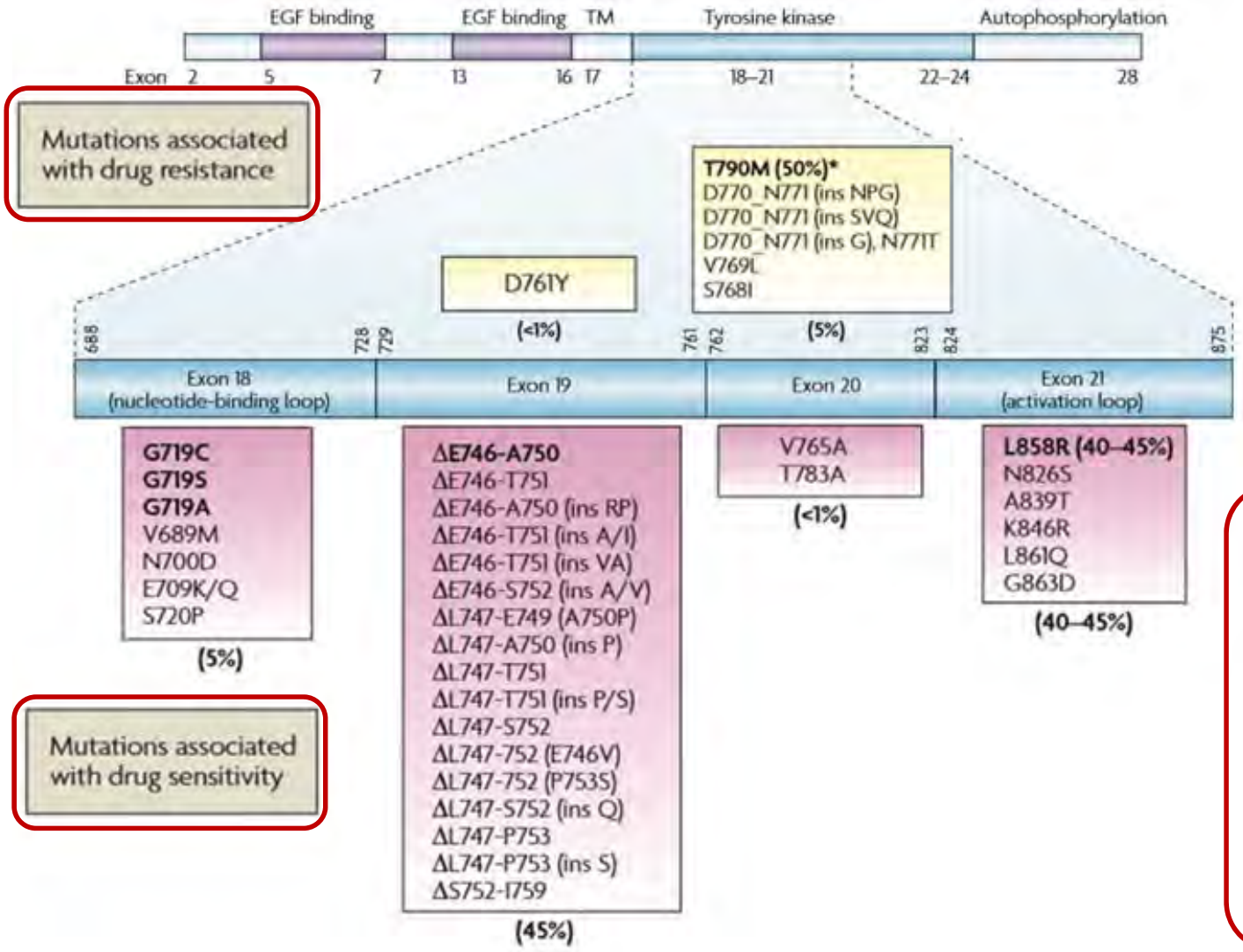
Protein kinase inhibitors (PKI) – 1.

Drugs	Molecular target	Indication
BCR/ABL inhibitors		
Imatinib	BCR/ABL, PDGFR, FIP1L1-PDGFRα, KIT	Ph+ chronic myeloid leukemia, Ph+ acute lymphoblastic leukemia, myelodysplastic/myeloproliferative diseases, hypereosinophilic syndrome, GIST, dermatofibrosarcoma protuberans
Dasatinib	BCR/ABL, Src family, KIT, EPHR, PDGFRβ,	Ph+ chronic myelogenous leukemia resistant to imatinib, Ph+ acute lymphoblastic leukemia, chronic myeloid leukemia in lymphoid blast phase, resistant to previous therapy
Nilotinib	BCR/ABL, PDGFR, KIT, EPHR	Ph+ chronic myeloid leukemia resistant to previous treatments including imatinib
Bosutinib	Src/ABL, BCR/ABL	Ph+ chronic myeloid leukemia resistant to previous treatments
Ponatinib	BCR-ABL	Ph+ Chronic myeloid leukemia or acute lymphoblastic leukemia with T315I mutation, Ph+ chronic myeloid leukemia or acute lymphoblastic leukemia for whom no other tyrosine kinase inhibitor therapy is indicated

BCR/ABL: BCR, RhoGEF and GTPase activating protein/ABL proto-oncogene 1, non-receptor tyrosine kinase; EPHR: ephrin receptor; FIP1L1-PDGFRα, factor interacting with PAPOLA and CPSF1 (FIP1L1) and platelet derived growth factor receptor alpha fusion protein (PDGFRα); KIT: KIT proto-oncogene receptor tyrosine kinase; PDGFR: platelet derived growth factor receptor ; Src: SRC proto-oncogene, non-receptor tyrosine kinase

From: Farmacologia - Principi di base e applicazioni terapeutiche (Rossi, Cuomo, Riccardi ed.) Chapter 9, Danesi, Mazzei, Mini, 2016

EGFR mutations in NSCLC



- EGFR mutations were initially reported in 2004 and currently define the most prevalent actionable genomically classified subgroup of NSCLC
- The most frequent EGFR mutations are depicted in Figure
- EGFR mutations are more frequent in:
  - tumors with adenocarcinoma histology
  - never smokers with NSCLC
  - Women
  - East-Asian patients

Frequencies and Types of EGFR Mutations in NSCLC

Sharma SV et al., Nat Rev Cancer, 2007

First- & second-generation EGFR inhibitors in NSCLC

Name	Generation	Inhibition type	Other HER kinases	Status
Erlotinib	I	Reversible	-	Approved
Gefitinib	I	Reversible	-	Approved
Afatinib	II	Irreversible	HER2/4	Approved
Dacomitinib (PF-00299804)	II	Irreversible	HER2/4	Phase III
Neratinib	II	Irreversible	HER2/4	Phase II

From Hirsch FR et al., Lancet, 2016, modified

Protein kinase inhibitors (PKI) – 2.

Drugs	Molecular target	Indication
EGFR inhibitors		
Gefitinib	EGFR	NSCLC with EGFR exon 19 deletions or EGFR exon 21 L858R mutation
Erlotinib	EGFR	NSCLC with EGFR exon 19 deletions or EGFR exon 21 L858R mutation, pancreatic carcinoma
Afatinib	EGFR, HER2, ErbB4	NSCLC with EGFR exon 19 deletions or EGFR exon 21 L858R mutation, squamous NSCLC
Lapatinib	HER2	HER2 overexpressing breast cancer
Osimertinib	EGFR	NSCLC with EGFR T790M mutation

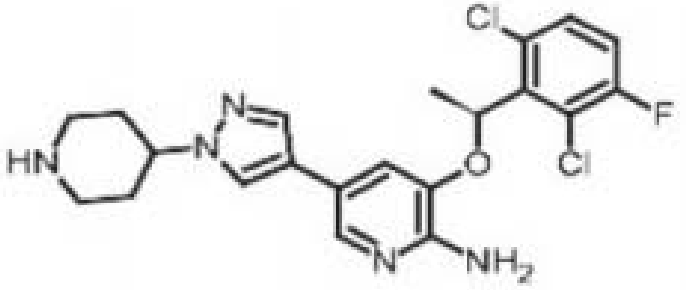
EGFR: epidermal growth factor receptor; HER2: erb-b2 receptor tyrosine kinase 2; ErbB4: erb-b2 receptor tyrosine kinase 4

From: Farmacologia - Principi di base e applicazioni terapeutiche (Rossi, Cuomo, Riccardi ed.) Chapter 9, Danesi, Mazzei, Mini, 2016

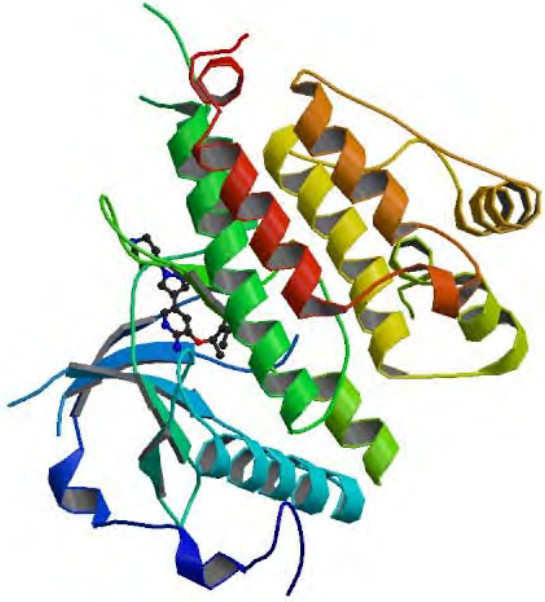
ALK gene rearrangements in NSCLC

- ***ALK*** **rearrangements are present in 3%–8% of NSCLC**
  - **More prevalent in non-smokers, younger patients, and adenocarcinomas**
  - **Usually mutually exclusive with *EGFR* or *KRAS* mutation**
- **A multi-target tyrosine kinase inhibitor**
- **Primarily developed as a MET inhibitor (IC_{50} , 11.0 nM)**
- **Higher affinity for ALK and ROS1 (IC_{50} 0.6 nM and 0.11 nM, respectively)**

Crizotinib (PF-02341066)



$C_{21}H_{22}Cl_2FN_5O$
MW 450.34
3-benzyloxy-2-aminopyridine



Structure of the human anaplastic lymphoma kinase (ALK) in complex with crizotinib

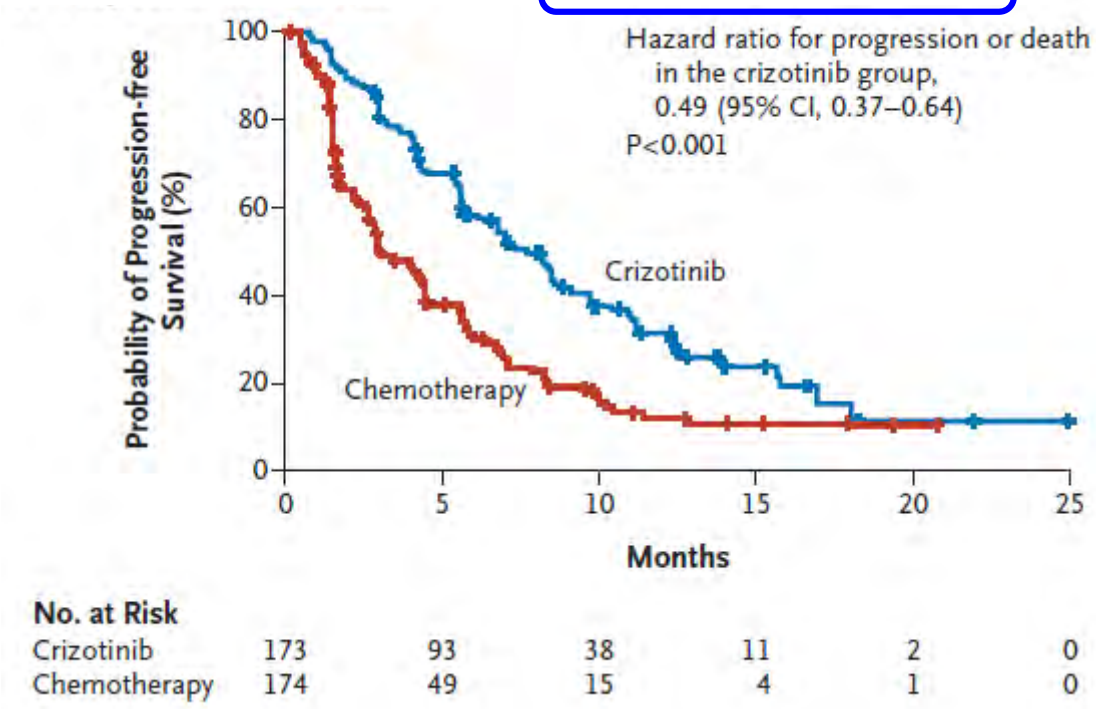
From Davies et al., Clin Cancer Res 2012;
Swanton & Govidan, NEJM 2016; EMA

1st generation ALK inhibitors (crizotinib) for NSCLC

Trials	Patients	Agents	No.	ORR	PFS	P value	Refs.
Phase III PROFILE1007	Relapsed/ refractory	Crizotinib vs Pemetrexed/ docetaxel	173 174	65 % 20 % Δ 45%	7.7 ms 3.0 ms Δ 4.7 ms	<0.001	Shaw NEJM, 2013
Phase III PROFILE1014	Untreated	Crizotinib vs Chemotherapy	172 171	74 % 45 % Δ 29%	10.9 ms 7.0 ms Δ 3.9 ms	<0.001	Solomon, NEJM, 2014

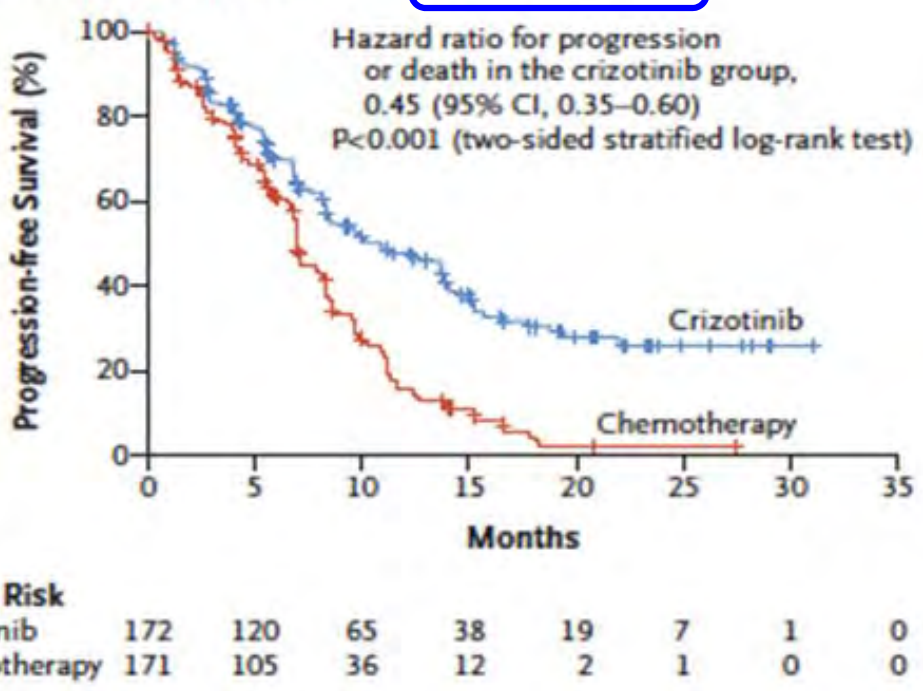
WU J et al., J Hematol Oncol, 2016

A. Progression-free survival – relapsed/refractory pts



Shaw AT et al. NEJM 2013

B. Progression-free survival – untreated pts



Solomon BJ et al. NEJM 2014

Protein kinase inhibitors (PKI) – 3.

Drugs	Molecular target	Indication
ALK inhibitors		
Crizotinib	ALK	ALK-rearranged NSCLC
Ceritinib	ALK	Crizotinib resistant NSCLC with ALK rearrangements
Alectinib	ALK	Crizotinib resistant NSCLC with ALK rearrangements
mTOR inhibitors		
Temsirolimus	mTOR	Renal cancer, mantle cell lymphoma
Everolimus	mTOR	Renal cancer, breast cancer, neuroendocrine pancreatic tumor
BRAF inhibitors		
Vemurafenib	BRAF V600E	Melanoma with BRAF V600E or V600K mutation
Dabrafenib	BRAF V600E, BRAF V600K	Melanoma with BRAF V600E or V600K mutation
MEK inhibitors		
Trametinib	MEK1/2	Melanoma with BRAF V600E or V600K mutation
Cobimetinib	MEK1/2	Melanoma with BRAF V600E or V600K mutation

ALK: Anaplastic lymphoma tyrosine kinase receptor; BRAF, B-Raf proto-oncogene, serine/threonine kinase, MEK1/2: mitogen-activated protein kinase 1/2; mTOR: mammalian target of rapamycin

From: Farmacologia - Principi di base e applicazioni terapeutiche (Rossi, Cuomo, Riccardi ed.) Chapter 9, Danesi, Mazzei, Mini, 2016

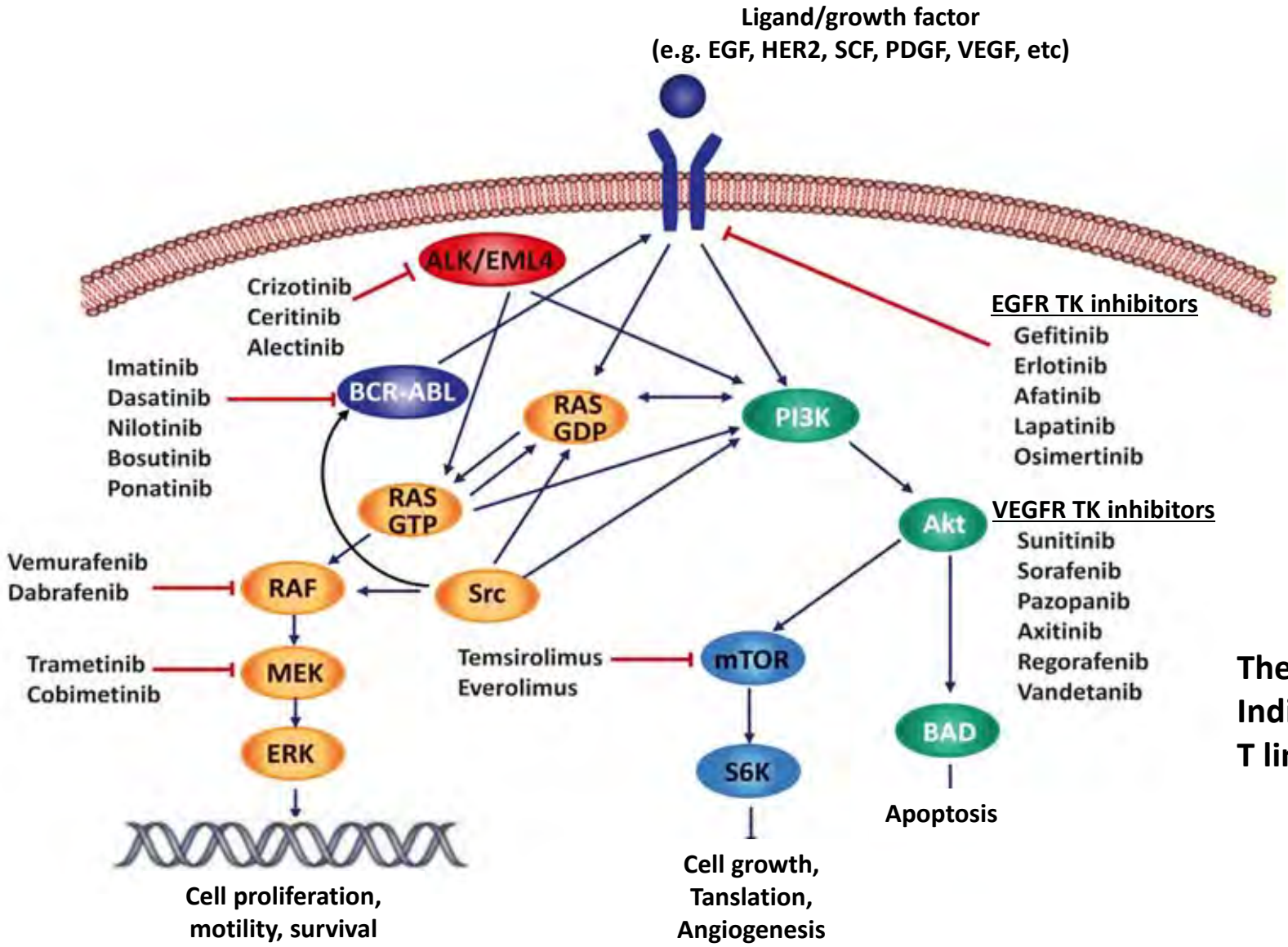
Protein kinase inhibitors (PKI) – 4.

Drugs	Molecular target	Indication
VEGFR inhibitors		
Sunitinib	Kit, PDGFR, FLT3, VEGFR2	GIST resistant to imatinib, renal cancer, neuroendocrine pancreatic tumor
Sorafenib	RAF-1, B-RAF, B-RAF V600E, KIT, FLT3, RET, VEGFR2, VEGFR3, PDGFRβ	Hepatocellular carcinoma, renal cancer, thyroid cancer
Pazopanib	VEGFR1-3, PDGFRα/β, FGFR-1 e 3, KIT	Renal cancer, soft-tissue sarcoma
Axitinib	VEGFR1-3	Renal cancer
Regorafenib	RET, VEGFR1-3, KIT, PDGFR-α/β, FGFR1-2, TIE2, DDR2	Colorectal cancer, GIST
Vandetanib	RET, BRK, TIE2, EGFR, VEGFR	Medullary thyroid cancer
Cabozantinib	RET, MET, VEGFR1-3, KIT, TRKB, FLT-3, AXL, and TIE2	Medullary thyroid cancer
Lenvatinib	VEGFR1, VEGFR2, VEGFR3	Differentiated thyroid cancer

AXL, AXL receptor tyrosine kinase; BRAF, B-Raf proto-oncogene, serine/threonine kinase; BRK, tyrosine kinase protein 6; DDR2: discoidin domain receptor tyrosine kinase 2; FGFR 1-3: fibroblast growth factor receptor 1-3; FLT3: Fms related tyrosine kinase 3; KIT: KIT proto-oncogene receptor tyrosine kinase; RET: Glial cell line-derived neurotrophic factor receptor; TIE2: TEK receptor tyrosine; TRKB: Tropomyosin receptor kinase B; VEGFR1-3: vascular endothelial growth factor receptor, 1-3

From: Farmacologia - Principi di base e applicazioni terapeutiche (Rossi, Cuomo, Riccardi ed.) Chapter 9, Danesi, Mazzei, Mini, 2016

Schematic diagram showing mechanisms of action of protein kinase inhibitors



The arrows
Indicate stimulation and the
T lines inhibition

From: Farmacologia - Principi di base e applicazioni terapeutiche (Rossi, Cuomo, Riccardi ed.) Chapter 9, Danesi, Mazzei, Mini, 2016

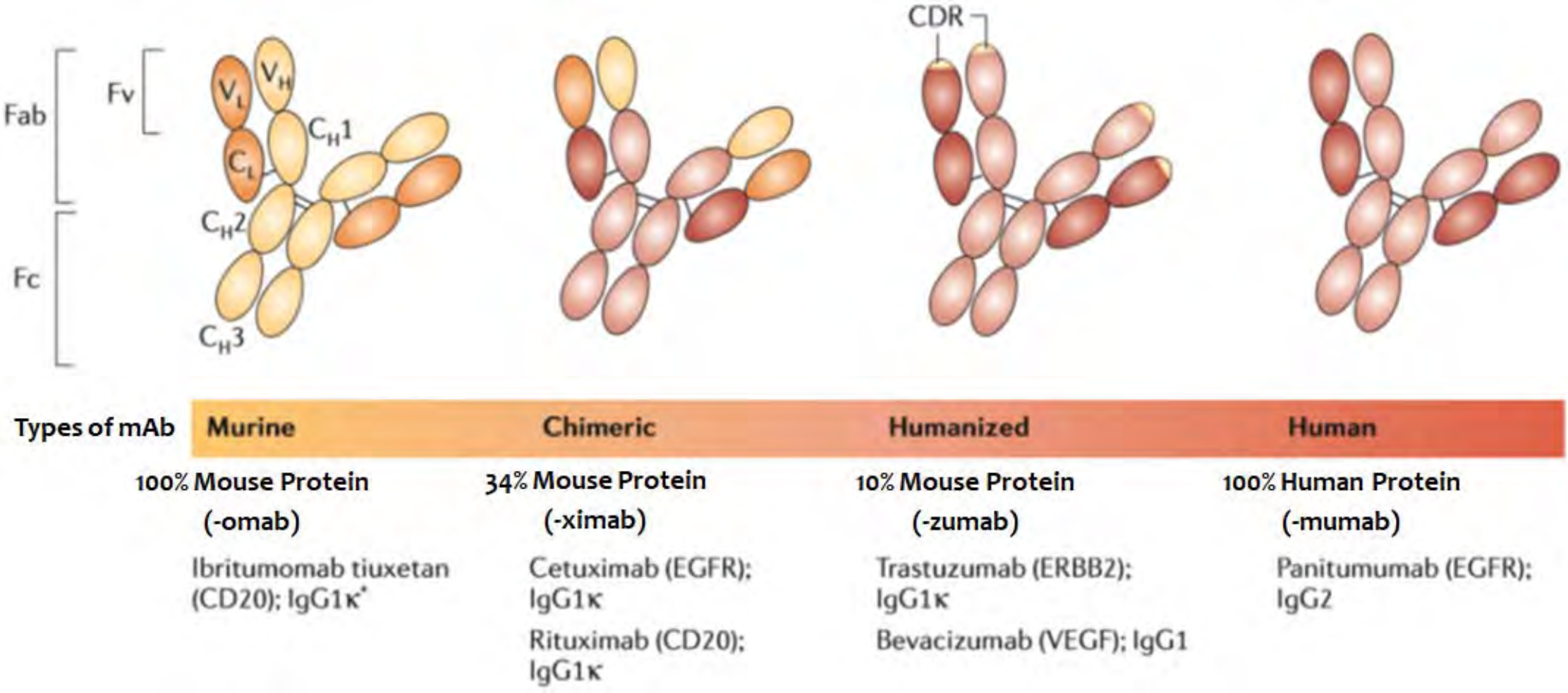
Major classes of cancer therapeutics – 3. Monoclonal antibodies

Murine ---> Fully Human

Molecularly directed development
Discovery based on receptors
Extracellular action
Cytostatic effect (reversible or irreversible)
Selective (less toxic)
Cyclic administration (following Minimum Effective Dose)
~ 150 kDa MW
i.v. (s.c.)

From Jimeno A et al. Curr Cancer Ther Rev, 2005 modified

The classification of therapeutic monoclonal antibodies (mAbs) by the different antibody types

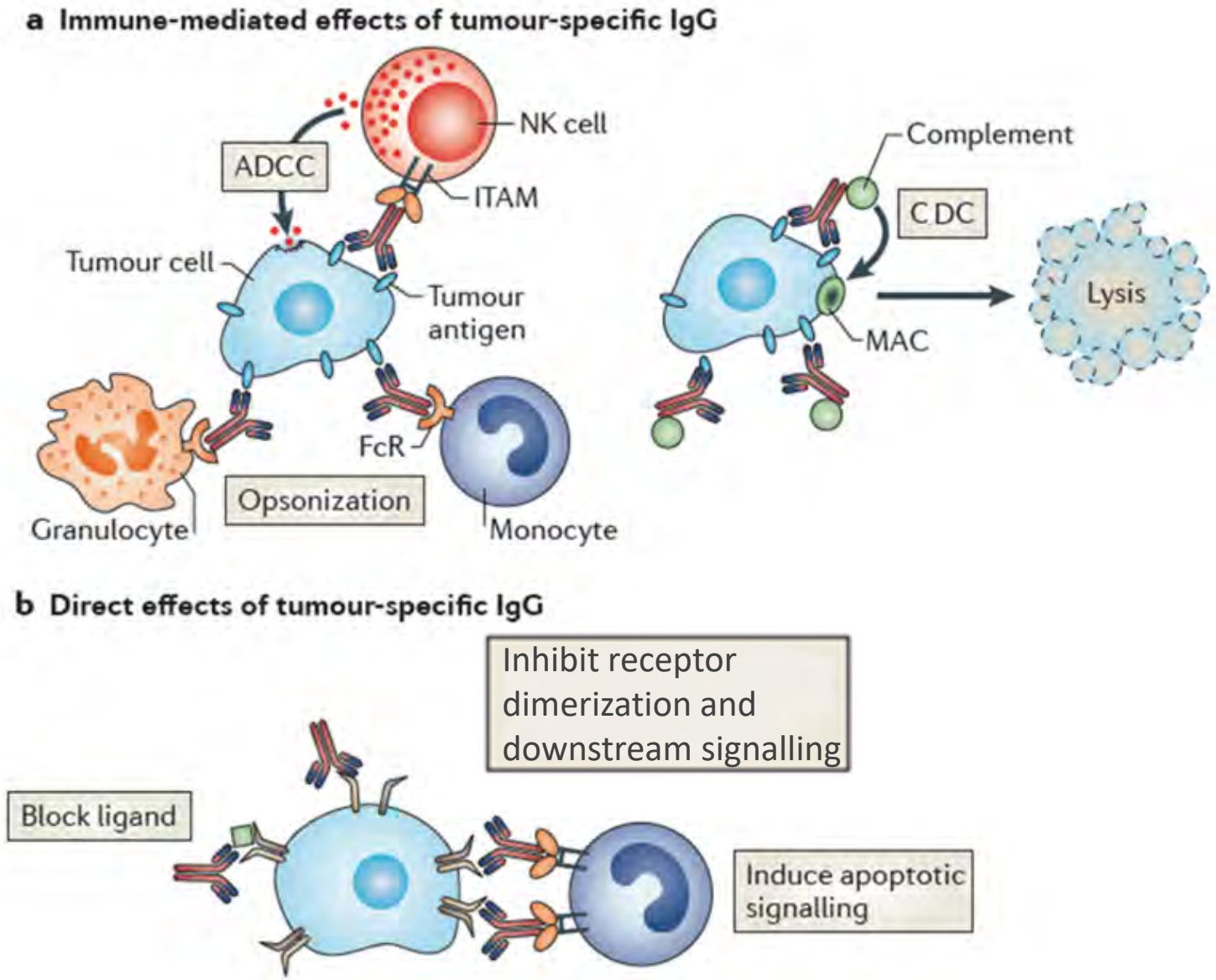


Types of mAb	Murine	Chimeric	Humanized	Human
	100% Mouse Protein	34% Mouse Protein	10% Mouse Protein	100% Human Protein
	(-omab)	(-ximab)	(-zumab)	(-mumab)
	Ibritumomab tiuxetan (CD20); IgG1κ*	Cetuximab (EGFR); IgG1κ	Trastuzumab (ERBB2); IgG1κ	Panitumumab (EGFR); IgG2
		Rituximab (CD20); IgG1κ	Bevacizumab (VEGF); IgG1	

Fab, antigen binding portion; Fc, effector portion; CDR, complementarity-determining regions

Imai K & Takaoka A, Nat Rev Cancer, 2006

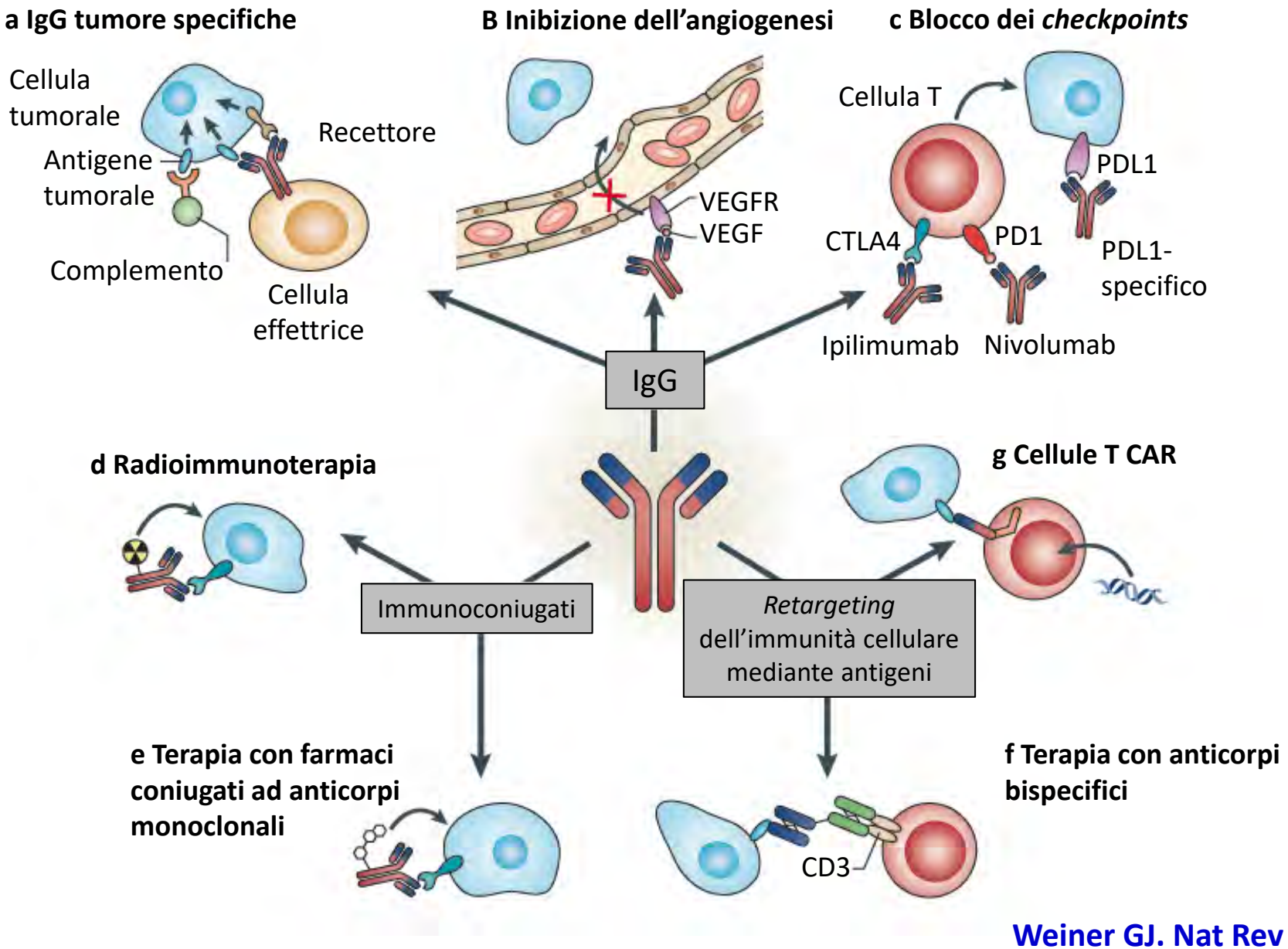
Mechanisms of action of monoclonal antibodies that target cancer cells



ACDC, antibody-dependent cellular cytotoxicity; CDC, Complement-dependent cytotoxicity; MAC, membrane attack complex; ITAM, immunoreceptor tyrosine-based activation motifs; NK, natural killer

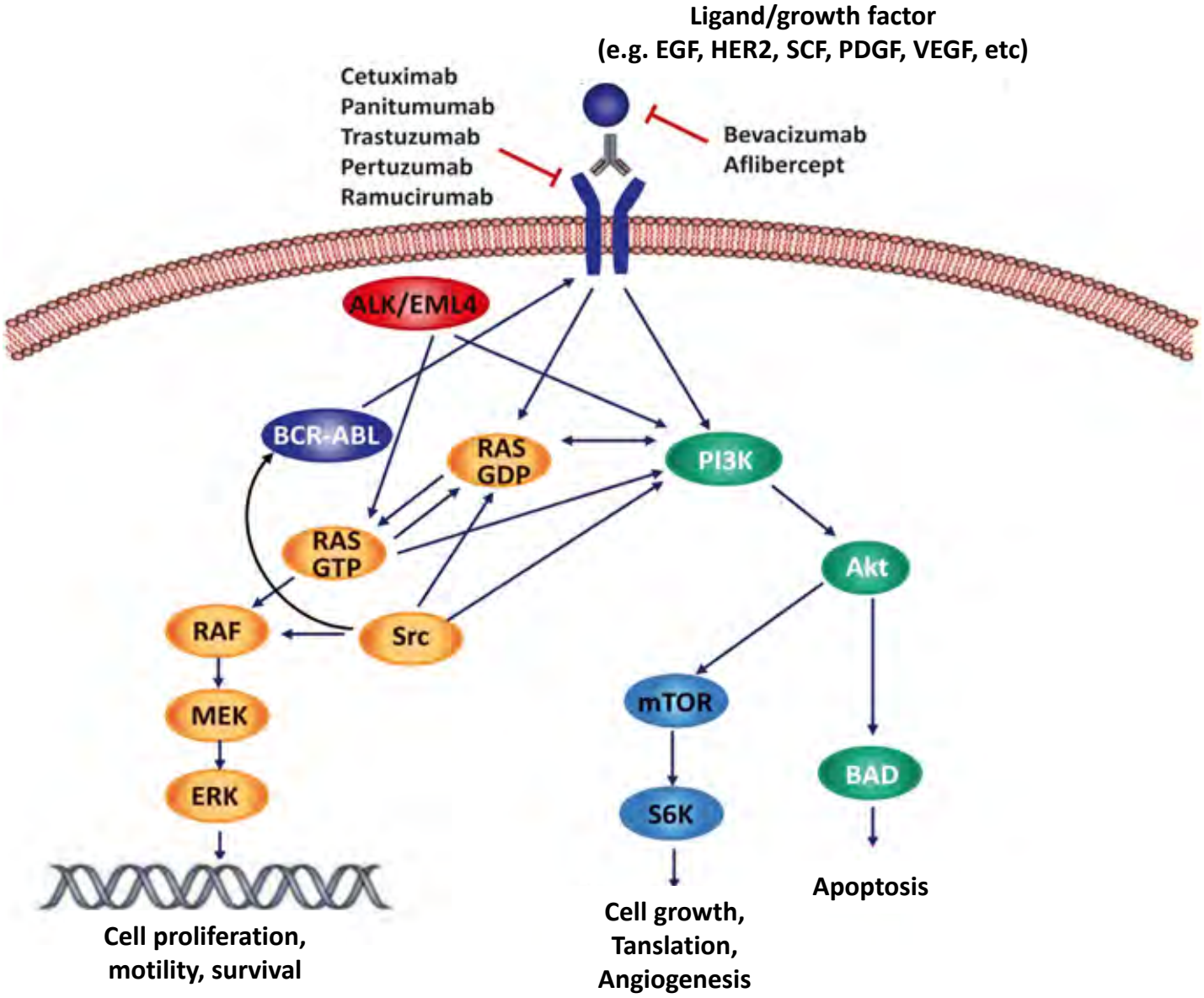
From Weiner GJ. Nat Rev Cancer, 2015, modified

Strategie terapeutiche antitumorali basate sull'impiego di anticorpi monoclonali



Weiner GJ. Nat Rev Cancer, 2015

Schematic diagram showing mechanisms of action of monoclonal antibodies



The arrows
Indicate stimulation and the
T lines inhibition

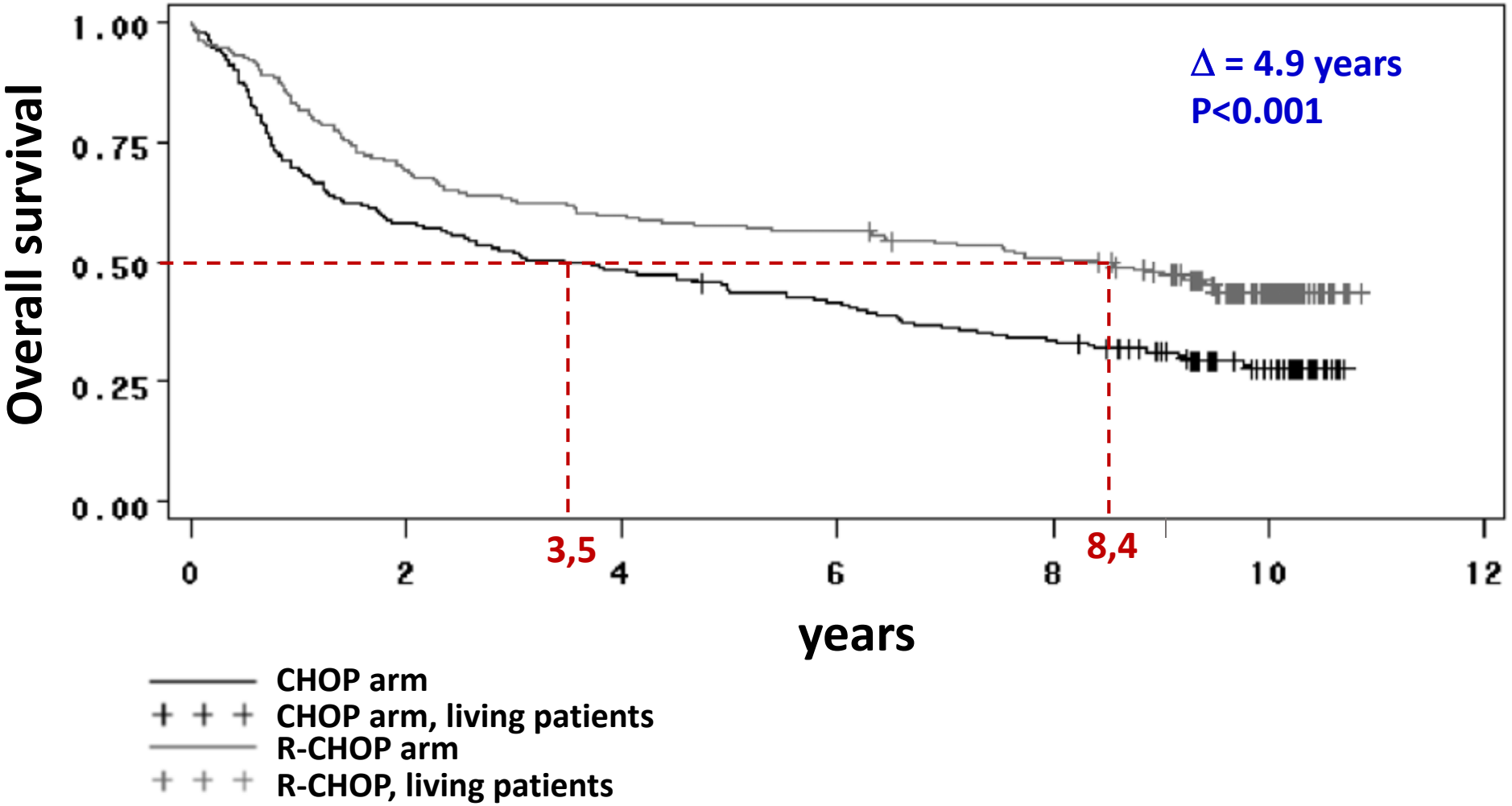
From: Farmacologia - Principi di base e applicazioni terapeutiche (Rossi, Cuomo, Riccardi ed.) Chapter 9, Danesi, Mazzei, Mini, 2016

FDA approved MoAbs – Hematology

Drug	Initial approval	Target/Biomarker	Type	Indication
Rituximab	1997	CD-20	Chimeric IgG1	NHL, CLL
^{90}Y-labelled Ibritumomab tiuxetan	2002	CD-20	Murine IgG1	relapsed or refractory, low-grade or follicular B-cell NHL; previously untreated follicular NHL
Ofatumumab	2009	CD-20	Human IgG1	CLL
Brentuximab vedotin	2011	CD-30/microtubule	Chimeric IgG1, auristatin-conjugated	HL and ALCL
Obinutuzumab	2013/2016	CD20	Humanized IgG1	CLL; follicular lymphoma
Blinatumomab	2014	Bispecific CD19-directed CD3 T-cell engager	Murine	Ph- relapsed or refractory B cell precursor ALL
Siltuximab	2014	IL-6	Chimeric IgGK	Multicentric Castelman's disease
Daratumumab	2015	CD-38	Human IgGK	Multiple myeloma
Elotuzumab	2015	SLAMF7	Humanized IgGK	Multiple myeloma
Nivolumab	2016	PD-1/PD-L1	Human IgG4	Hodgkin lymphoma
Pembrolizumab	2017	PD-1	Humanized IgG4	Hodgkin lymphoma
Inotuzumab ozogamicin	2017	CD22	Humanized IgG4 calicheamicin conjugated	Relapsed or refractory B cell precursor ALL
Tisagenlecleucel	2017	CD19	CAR T cells (anti CD19)	B cell ALL
Axicabtagene ciloleucel	2017	CD19	CAR T cells (anti CD19)	DLBCL

NHL, non-Hodgkin lymphoma; CLL, Chronic lymphocytic leukemia; AML, acute myeloid leukemia; ALCL, anaplastic large cell lymphoma; ALL, Acute lymphoblastic leukemia; DLBCL, diffuse large B cell lmphoma

Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients



CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone ; R-CHOP, rituximab-CHOP

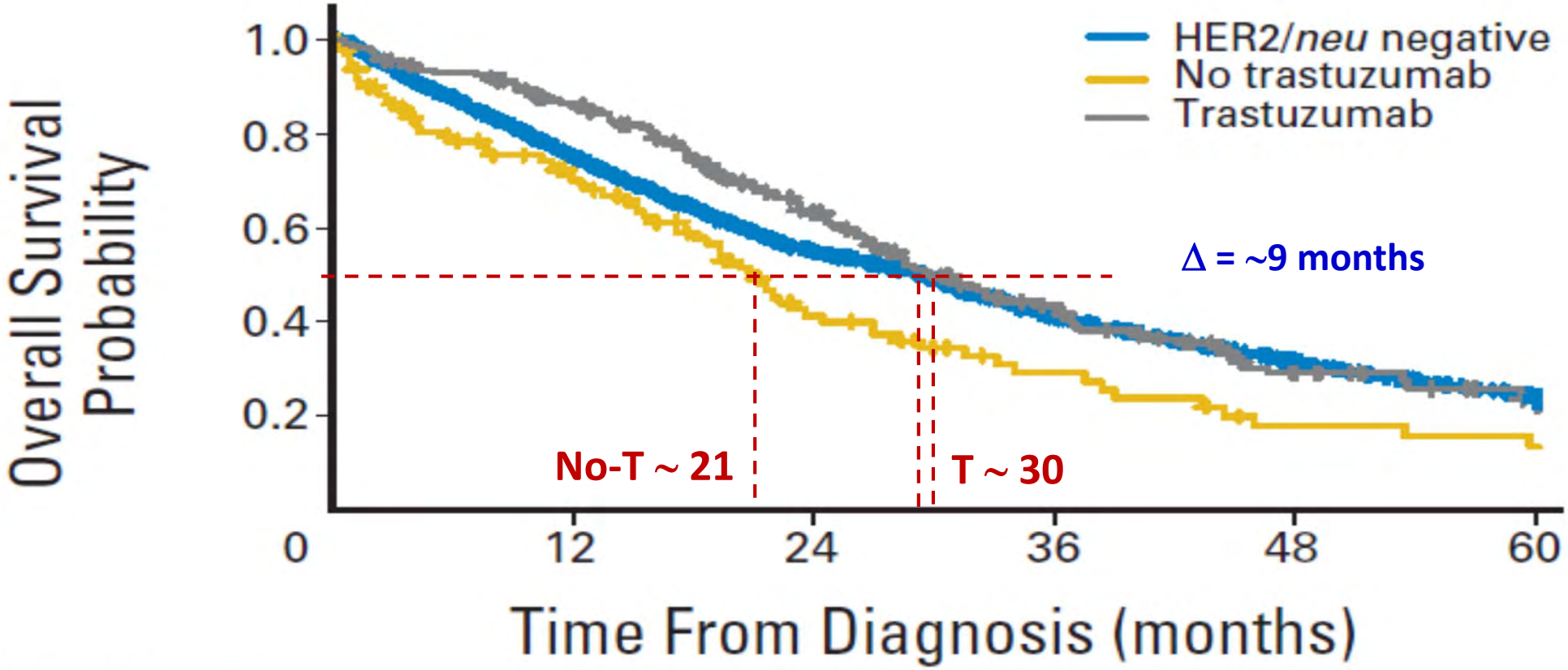
Coiffier et al., Blood 2010

FDA approved MoAbs – oncology (I)

Drug	Initial approval	Target/ Biomarker	Type	Indication
Trastuzumab	2000/2012	HER2/HER2	Humanized IgG1	Breast cancer/Gastric cancer
Cetuximab	2004/2008/2014	EGFR/KRAS/RAS	Chimeric IgG1	Colorectal cancer
Bevacizumab	2004-2016	VEGF	Humanized IgG1	Colorectal cancer- NSCLC- glioblastoma- renal cell carcinoma- epithelial ovarian, fallopian tube or primary peritoneal cancer
Panitumumab	2006-8/2013	EGFR/KRAS/RAS	Human IgG2	Colorectal cancer
Aflibercept	2012	VEGF-A/B, PIGF	Fc fusion	Colorectal cancer
Pertuzumab	2012	HER2/HER2	Humanized IgG1	Breast cancer
Ado-trastuzumab emtansine	2013	HER2/HER2	Humanized IgG1	Breast cancer
Ramucirumab	2014/2015	VEGFR2	Human IgG1	Gastric or gastro-esophageal junction adenocarcinoma, NSCLC/colorectal cancer
Necitumumab	2015	EGFR	Human IgG1	NSCLC
Olaratumab	2016	PDGFR-α	Human iGg1	Soft tissue sarcoma

Trastuzumab has changed the natural history of HER2-positive disease

Patients with HER2-positive mBC have comparable outcomes with HER2-negative mBC



No. of patients at risk						
HER2/*neu* negative	1,782	1,060	633	348	211	120
No trastuzumab	118	65	31	16	8	6
Trastuzumab	191	155	94	51	25	10

Dawood et al., J Clin Oncol, 2010

Types of medical therapy in oncology (III)

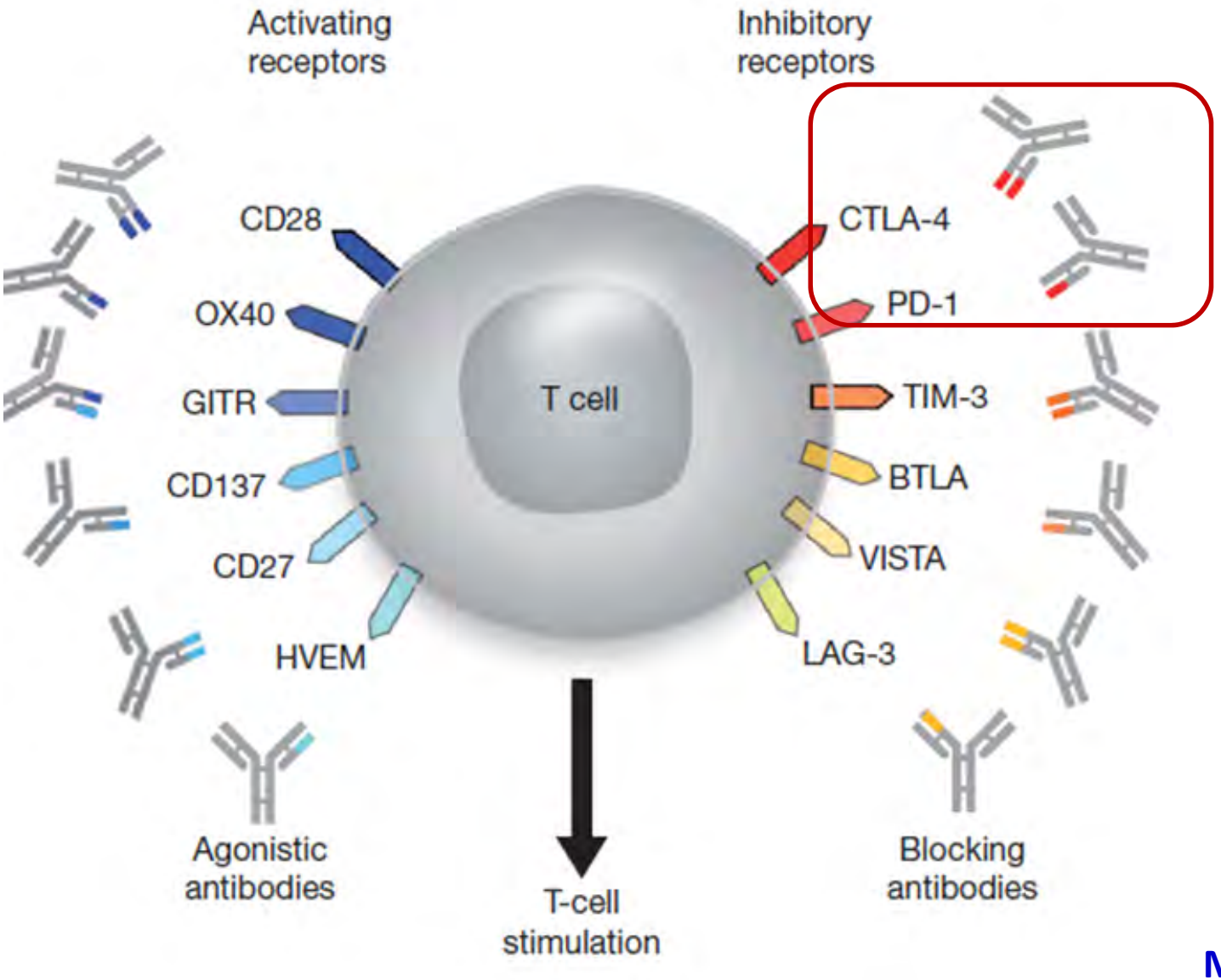
Immunotherapy →

- **Passive**: it consists of the transfer to the host of substances or effector cells capable to directly or indirectly mediate antitumor response
  - **Monoclonal antibodies** 'naked' (trastuzumab, …), conjugated (radiolabeled: ibritumomab tiuxetan; chemolabeled: brentuximab vedotin, ado- trastuzumab emtansine)
  - **Adoptive cell transfer:** chimeric antigen receptor (CAR) T cells (anti CD19 antigen)

→

- **Active**: it consists in host immunization with therapeutic agents that stimulate an intrinsic humoral and/or cell-mediated immune response capable of destroying tumor cells and/or prevent disease relapse
  - **Cancer vaccines:** dendritic cell-based vaccines (sipuleucel-T); peptide and DNA-based vaccines (under development)
  - **Immunomodulatory cytokines:** interleukin 2, interferon α2a and α2b
  - **Immunomodulatory monoclonal antibodies:** immune checkpoint inhibitors (ipilimumab, nivolumab, pembrolizumab…)
  - **Toll-like receptor (TLR) agonists:** Bacille Calmette-Guérin (BCG), imiquimod
  - **Other immunomodulatory drugs (IMiDs):** lenalidomide, pomalidomide, thalidomide

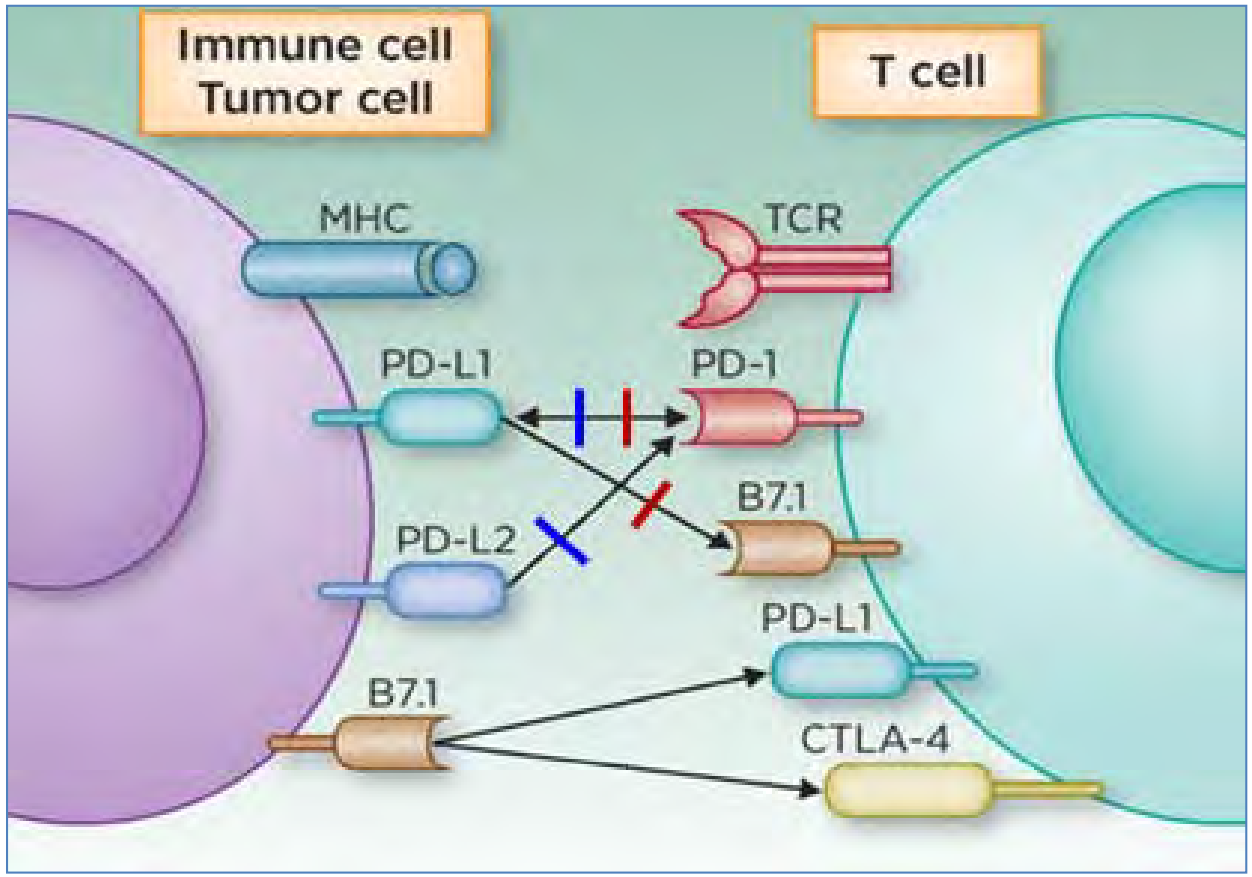
T cells as targets for immunoregulatory antibody therapy



Science, 2013

Mellman I et al., Nature, 2011

PD-1 pathway and immune surveillance



- PD-1 is a negative co-stimulatory receptor expressed primarily on activated T cells
- Binding of PD-1 to its ligands PD-L1 and PD-L2 inhibits effector T-cell function
- Expression of PD-L1 on tumor cells and macrophages can suppress immune surveillance and permit neoplastic growth
- Anti-PD-1/PD-L1 antibodies have demonstrated clinical activity in multiple tumor types

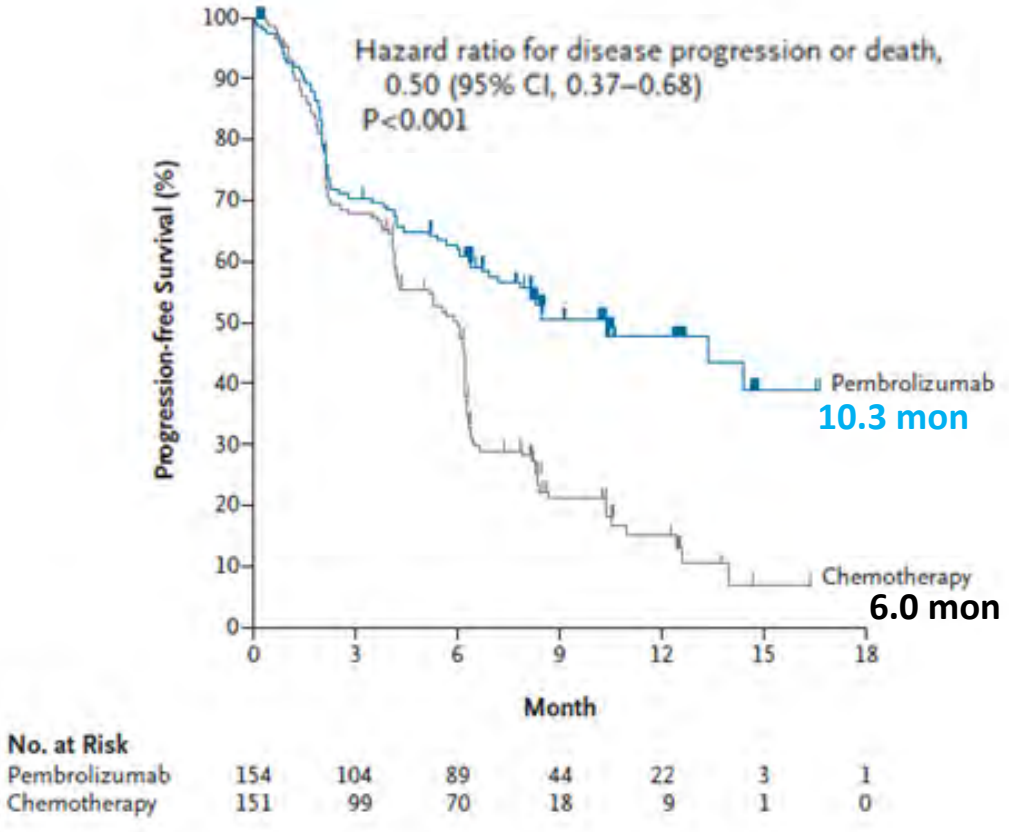
From Soria JC et al., Clin Cancer Res, 2015, modified

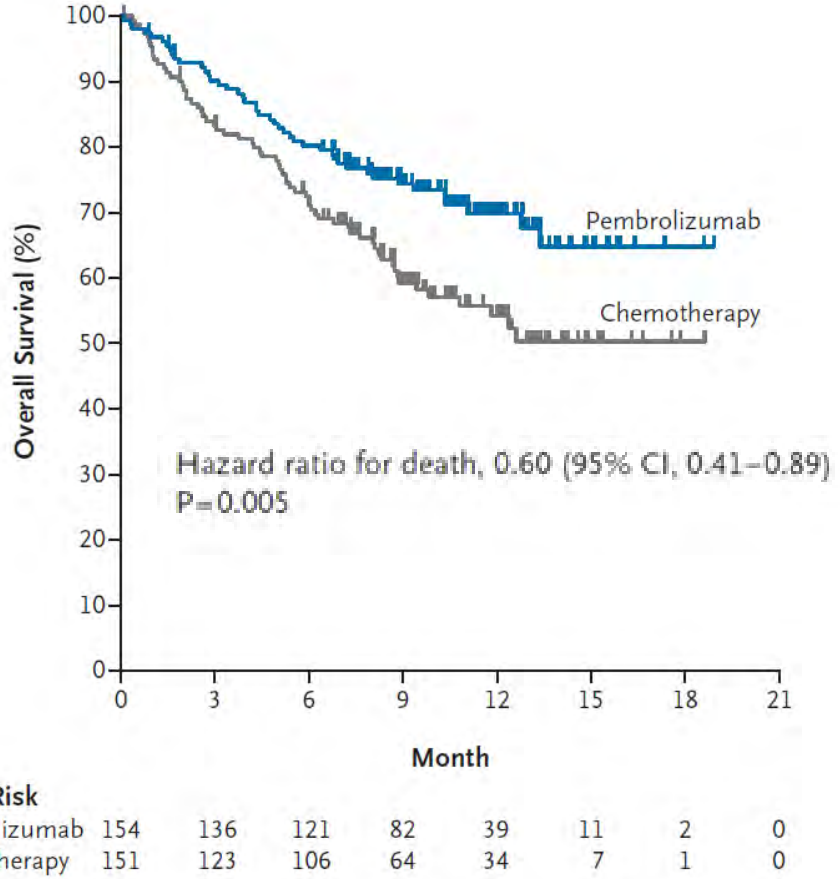
FDA approved MoAbs – oncology (II)

Drug	Initial approval	Target/ Biomarker	Type	Indication
Ipilimumab	2011	CTLA-4	Human IgG1	Melanoma
Nivolumab	2014-2016	PD-1	Human IgG4	Melanoma- NSCLC- SqCHNC – renal cancer – Hodgkin's lymphoma – urothelial carcinoma – MSI-H CRC
Pembrolizumab	2014-2016	PD-1/PD-L1	Humanized IgG4	Melanoma- NSCLC – SqCHNC – Hodgkin's lymphoma – urothelial carcinoma – MSI-H CRC – gastric carcinoma
Atezolizumab	2016/2017	PD-L1	Humanized IgG1	Urothelial carcinoma/NSCLC
Avelumab	2017	PD-L1	Human IgG1	Merkel cell carcinoma
Durvalumab	2017	PD-L1	Human IgG1κ	Urothelial carcinoma

Pembrolizumab versus chemotherapy for PD-L1 positive (≥50%) in previously untreated NSCLC and no EGFR sensitizing mutation or ALK translocation

PFS and OS in the intention-to-treat population





Reck M et al., N Engl J Med, 2016

Ormonoterapia

Types of medical therapy in oncology (IV)

Hormonal therapy: → Hormones and hormone antagonists:

- **Hormone supplementation:** administration of supraphysiologic doses of hormones – progestins, estrogens, androgens, corticosteroids and somatostatin analogs
- **Inhibition of hormone synthesis:** administration of agents inhibiting the synthesis of ligands (steroidal hormones, LH, FSH) - aromatase inhibitors and GnRH analogs
- **Antagonism of hormone receptors:** administration of agents competing at the level of the receptor with the ligand – antiestrogens, antiandrogens

Ormoni ed antagonisti utili in terapia oncologica

Ormoni e antagonisti		Indicazione
Glucocorticoidi	Prednisone	Leucemia linfocitica acuta e cronica, linfoma non Hodgkin, linfoma di Hodgkin, carcinoma della mammella, mieloma multiplo
Progestinici	Medrossiprogesterone acetato Megestrolo acetato	Carcinoma dell'endometrio, carcinoma della mammella
Antiestrogeni	Tamoxifene, Toremifene, Fulvestrant	Carcinoma della mammella
Antiandrogeni	Flutamide, Bicalutamide, Enzalutamide, Ciproterone acetato	Carcinoma prostatico
Inibitori dell'aromatasi	Anastrozolo, Letrozolo, Exemestane	Carcinoma della mammella
Inibitori del CYP450	Abiraterone	Carcinoma prostatico
Analoghi agonisti del GnRH	Buserelina, Leuprorelina, Goserelin, Triptorelina	Carcinoma prostatico
Analoghi antagonisti del GnRH	Degarelix	Carcinoma prostatico