TRAINING REGIONALE PER FARMACISTI OSPEDALIERI SU LEUCEMIA MIELOIDE CRONICA (LMC), NUOVE TECNOLOGIE ED APPROCCI

Roma, 16 Novembre 2015

La Targeted Therapy e l'appropriatezza terapeutica

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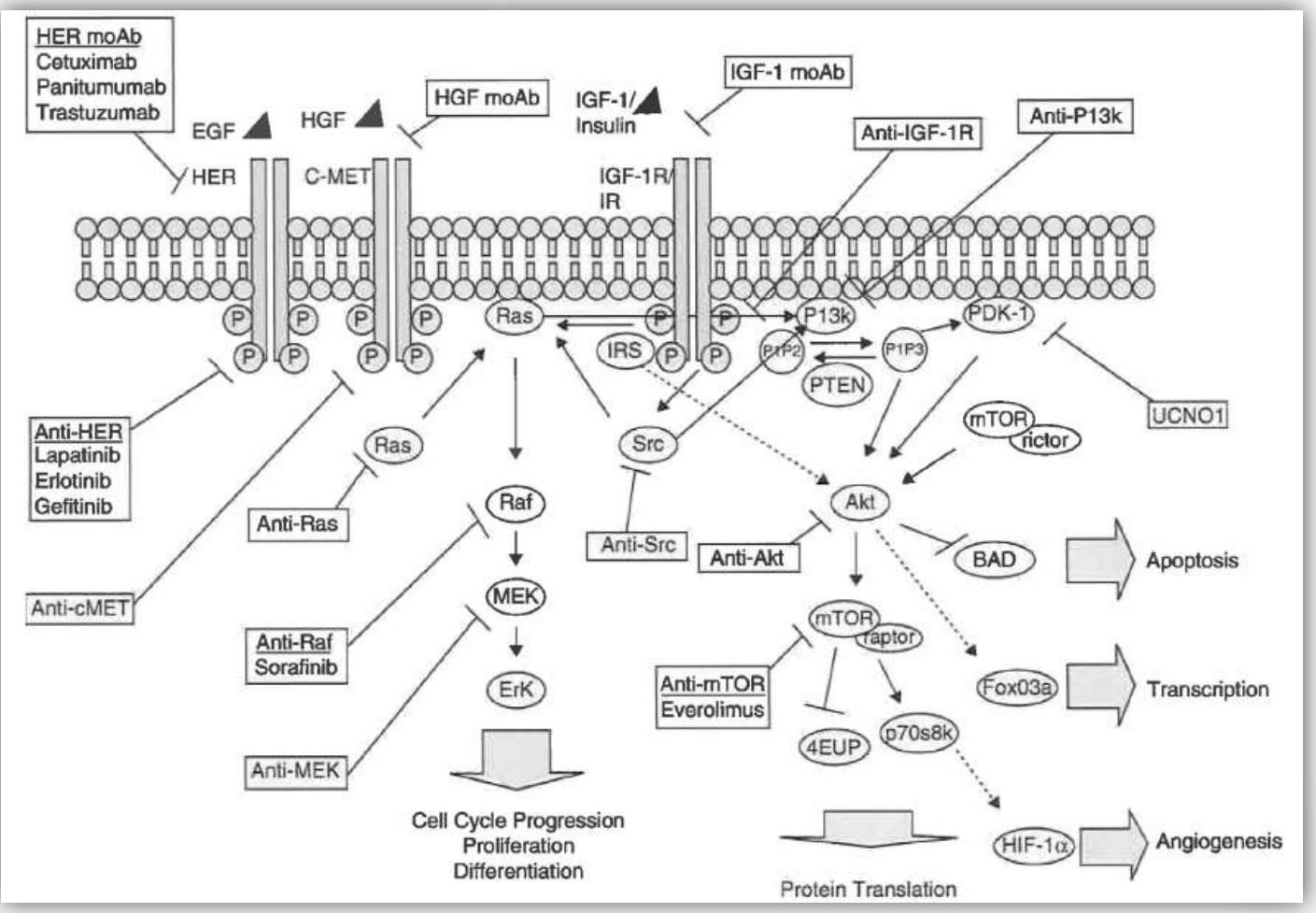
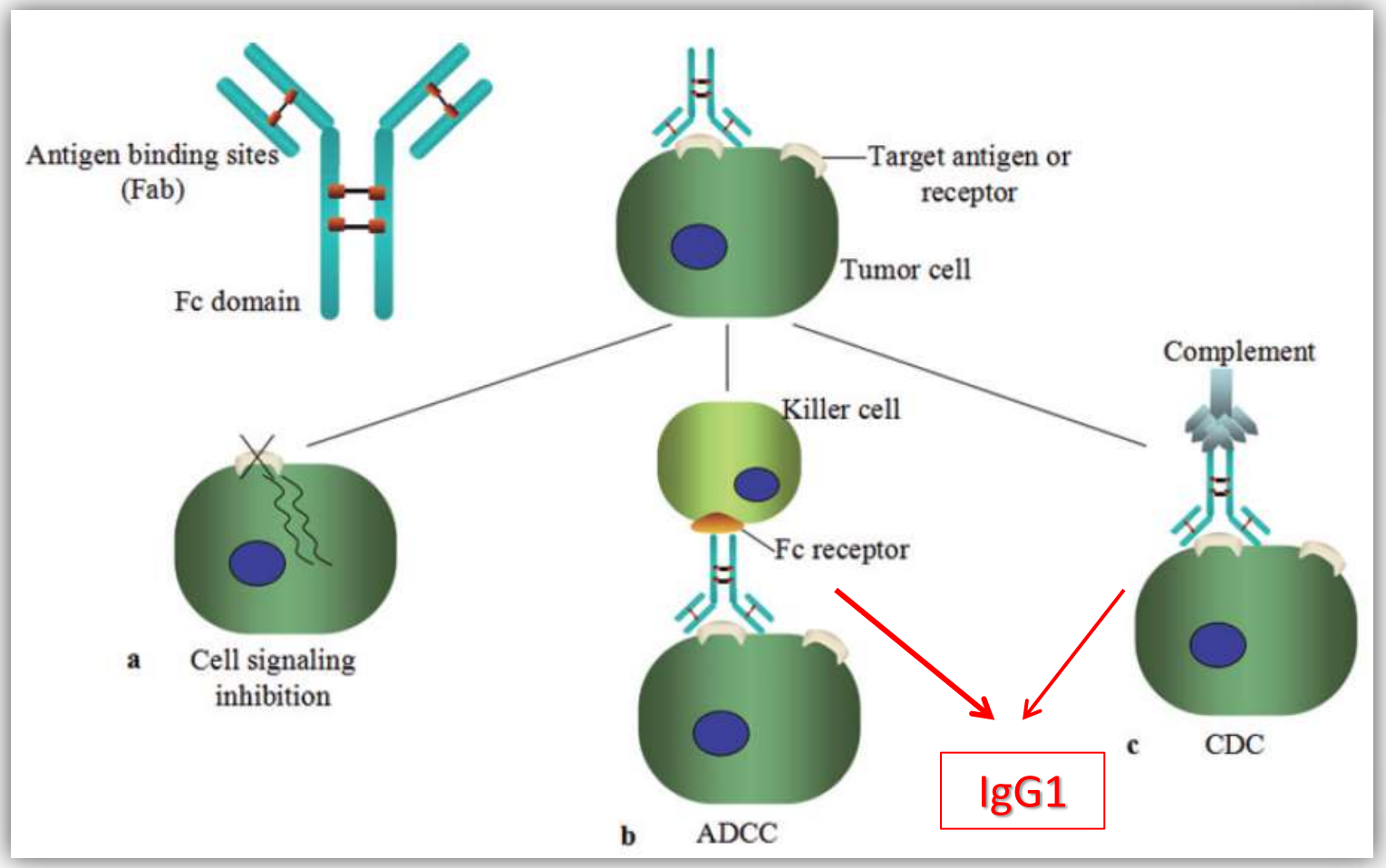
Targeted therapies

Drugs designed to interfere with dysfunctional signaling pathways that promote the growth of cancer cells (more selective and reduced toxicity).



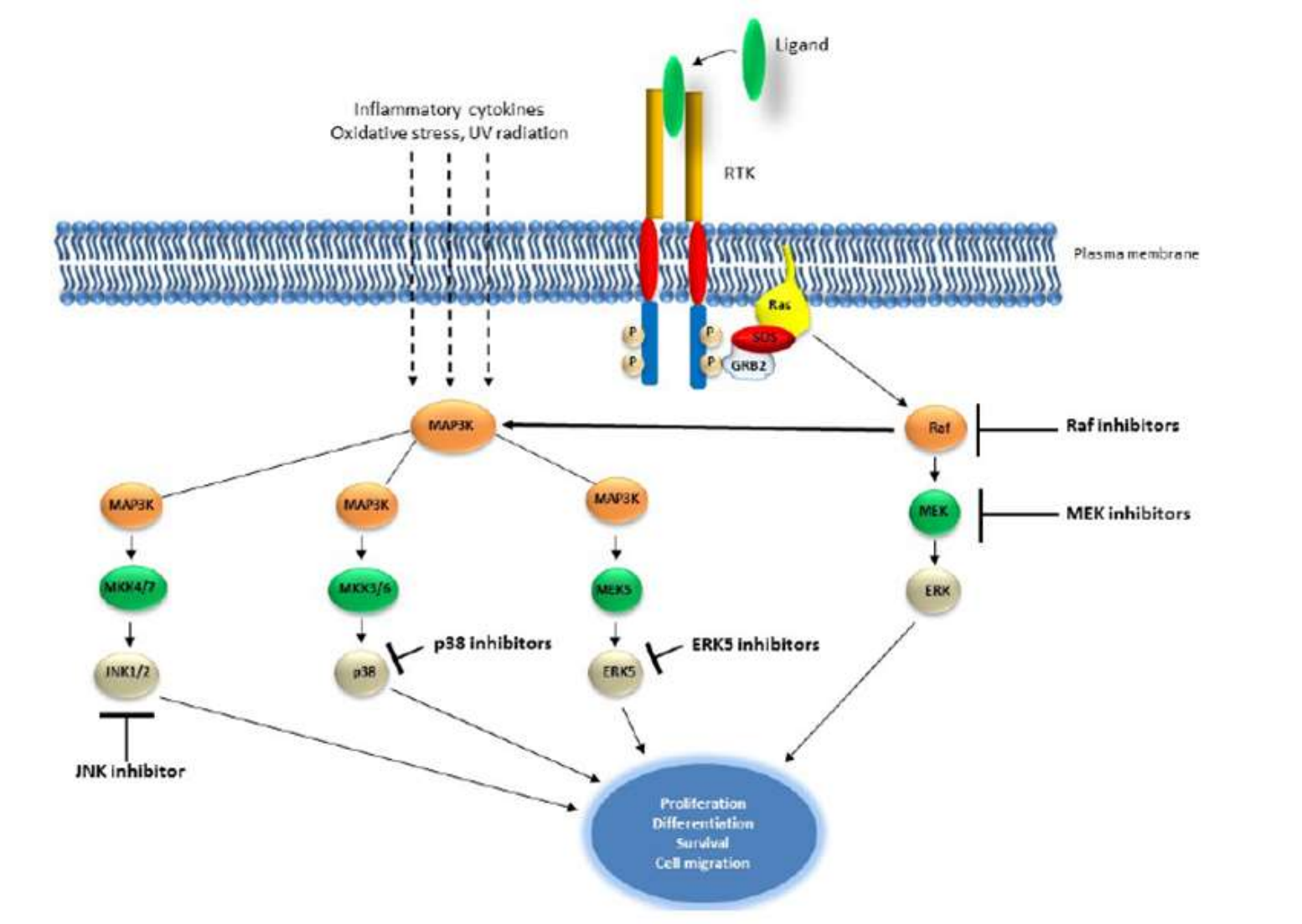
Wujcik D. Science and mechanism of action of targeted therapies in cancer treatment. Semin Oncol Nurs. 2014; 30: 139-146.

mAb: molecular mechanisms of action



Li GN, Wang SP et al. Monoclonal antibody-related drugs for cancer therapy. Drug Discov Ther. 2013; 7: 178-184.

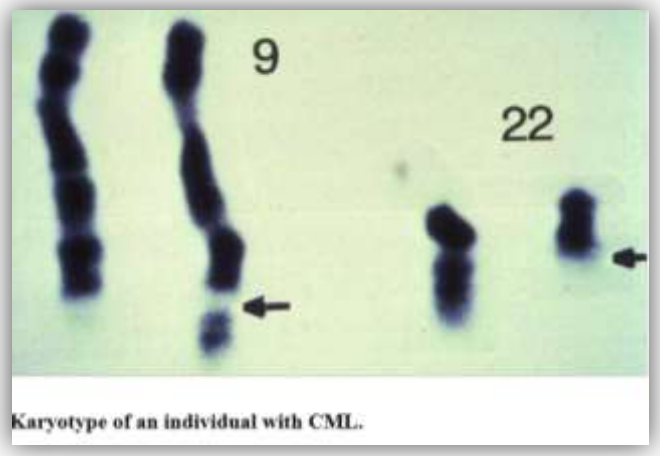
TKIs: moleculra mechanisms of action



Li GN, Wang SP et al. Monoclonal antibody-related drugs for cancer therapy. Drug Discov Ther. 2013; 7: 178-184.

CHRONIC MYELOID LEUKEMIA (CML)

Myeloproliferative disorder resulting from the clonal expansion of a transformed multipotent hematopoietic stem cell (HSC)



Karyotype of an individual with CML.

At chromosomal level: Philadelphia (Ph) Chromosome

*(Nowell P and Hungerford D. A minute chromosome in human chronic granulocytic leukemia [abstract]. Science **1960**; 132: 1497)*

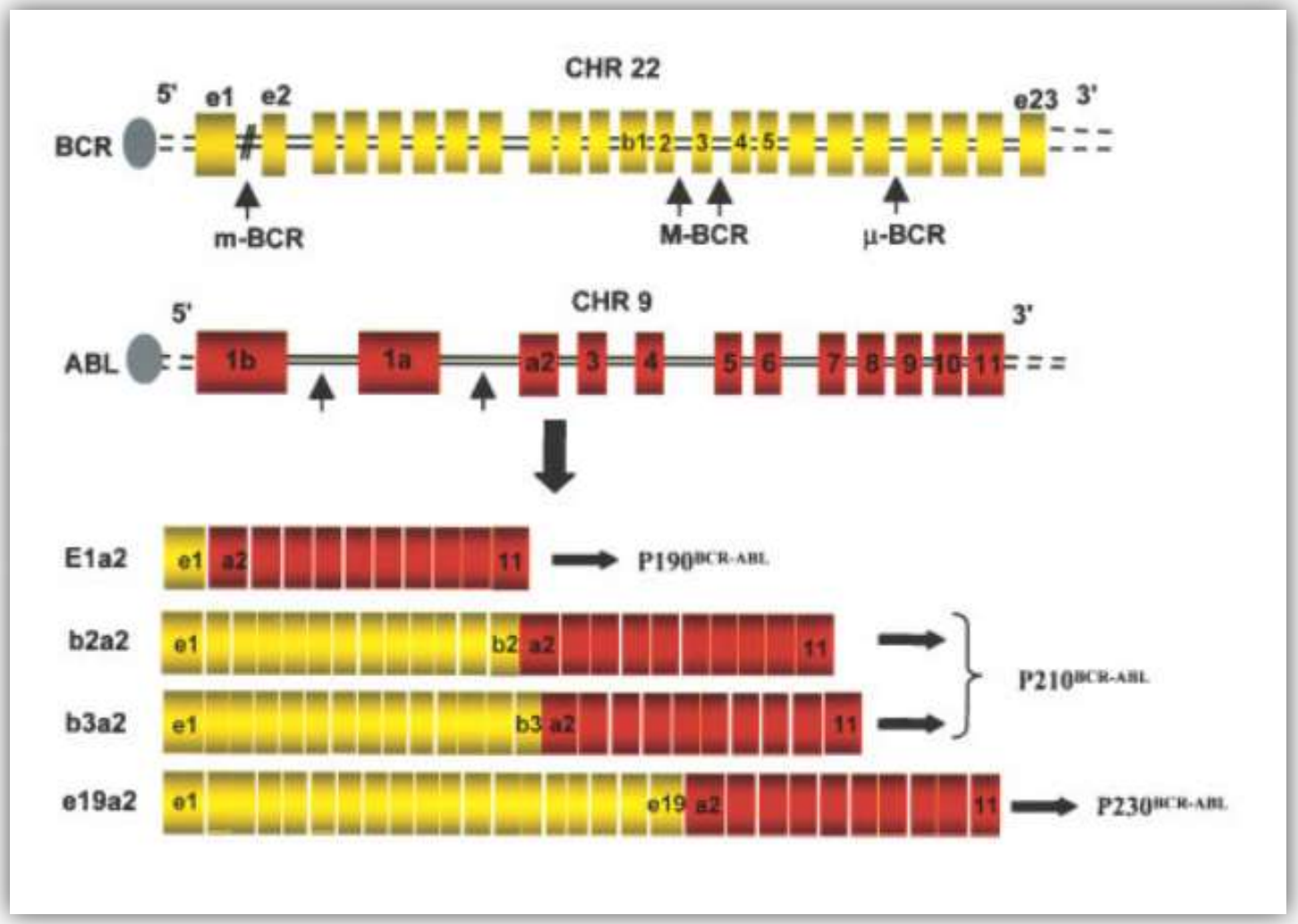
The Ph Chromosome arises from a t(9;22)(q34;q11) reciprocal chromosomal translocation

*(Rowley JD. Letter: A new consistent chromosomal abnormality in chronic myelogenous leukaemia identified by quinacrine fluorescence and Giemsa staining. Nature. **1973**; 243: 290-293.*

At molecular level: *fusion gene BCR-ABL*

*(Groffen J et al., Philadelphia chromosomal breakpoints are clustered within a limited region, bcr, on chromosome 22. Cell **1984**; 36: 93-99)*

BCR/ABL fusion genes



Salesse S, Verfaillie CM. BCR/ABL: from molecular mechanisms of leukemia induction to treatment of chronic myelogenous leukemia. Oncogene. 2002; 21: 8547-8559.

BCR/ABL tyrosine kinase

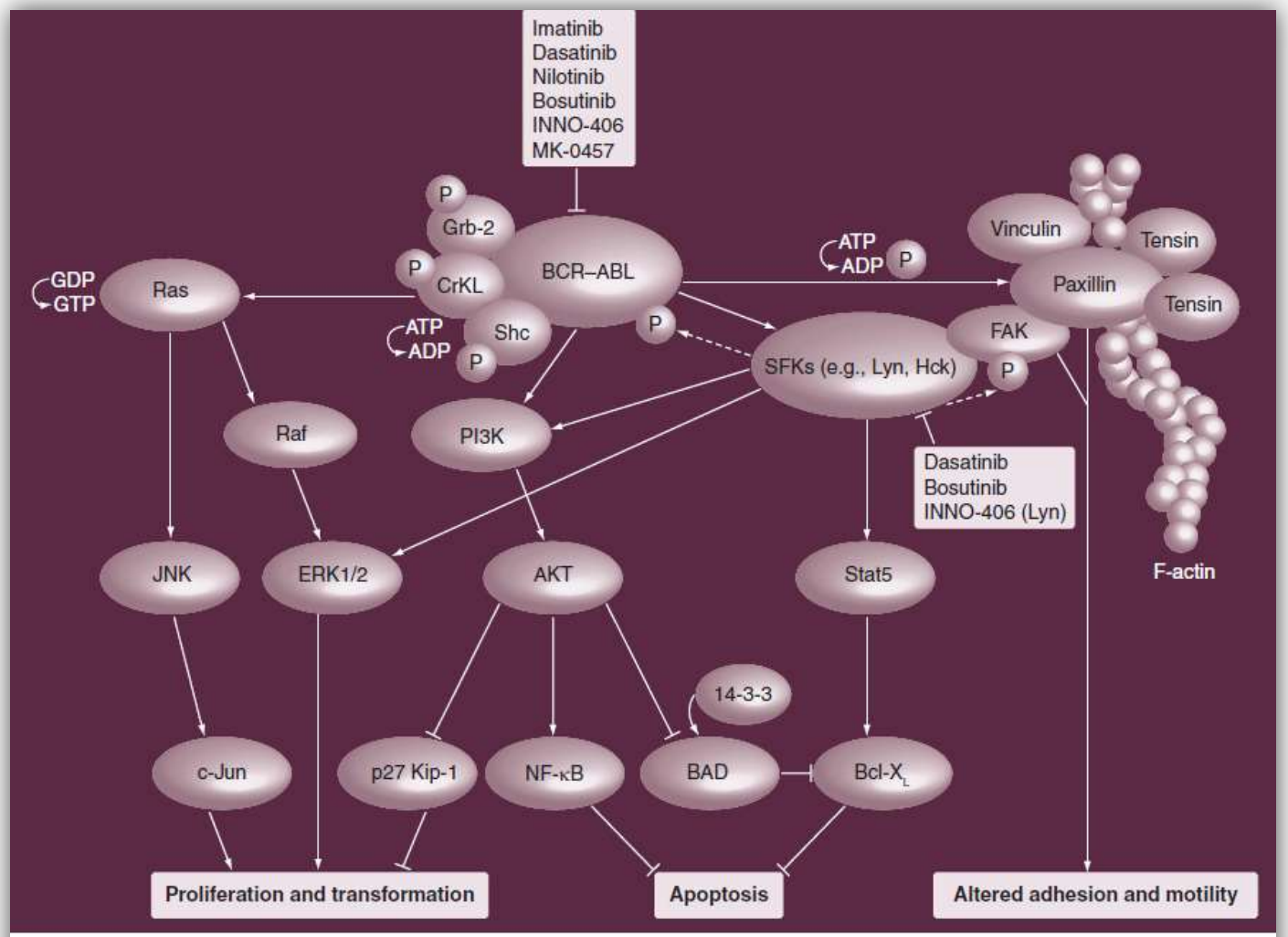


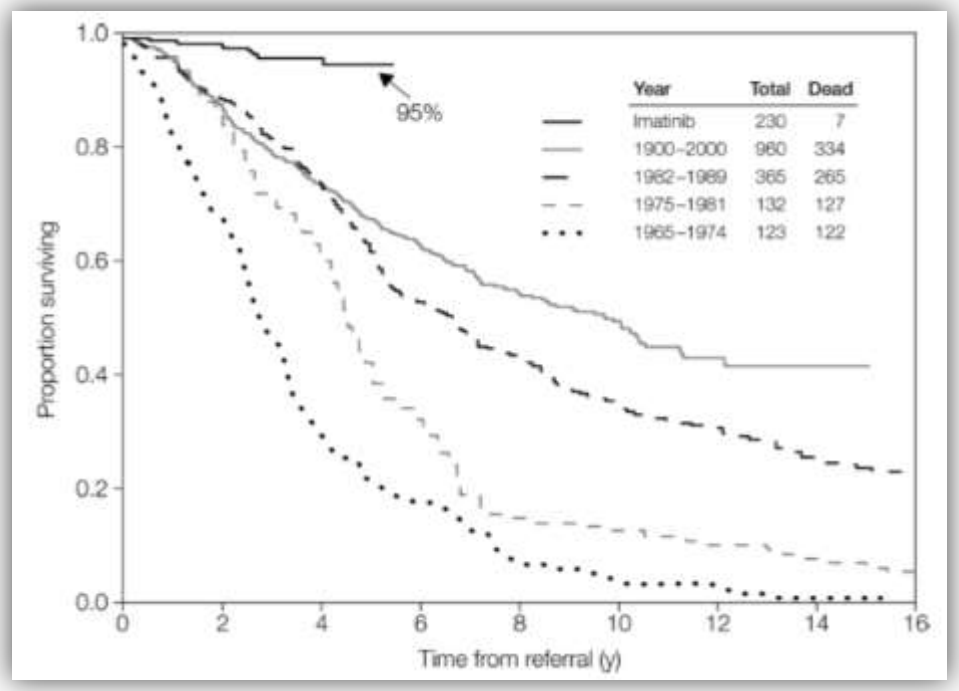
Figure 1. Molecular pathways involved in oncogenic Bcr–Abl signaling.
Adapted from [4].

Jabbour E, Cortes JE, Ghanem H, O'Brien S, Kantarjian HM. Targeted therapy in chronic myeloid leukemia. Expert Rev Anticancer Ther. 2008; 8: 99-110.

CML: towards a TARGETED-THERAPIES

1900 Spleen Irradiation → 1953 Oral Busulfan → 1972 Hydroxy-urea → 1975 Allogenic Hematopoietic SCT → 1985 IFNα → 1995 IFNα cytarabine

ABL/BCR TYROSIN KINASE INHIBITORS: IMATINIB (2001)

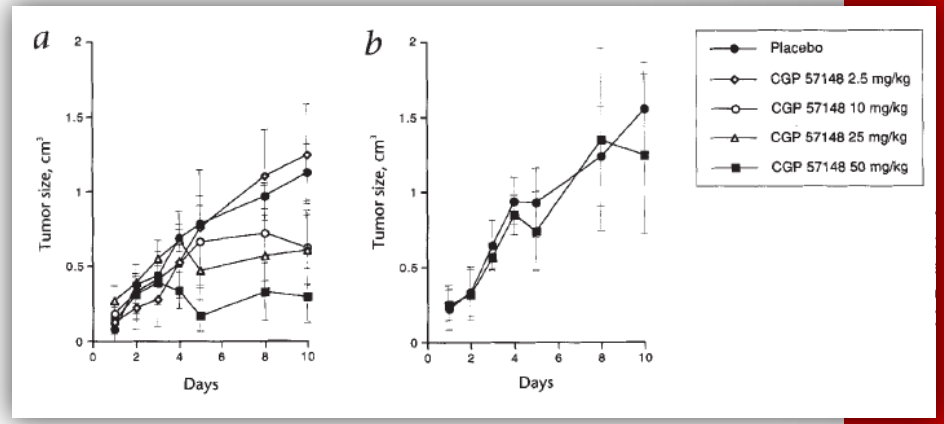


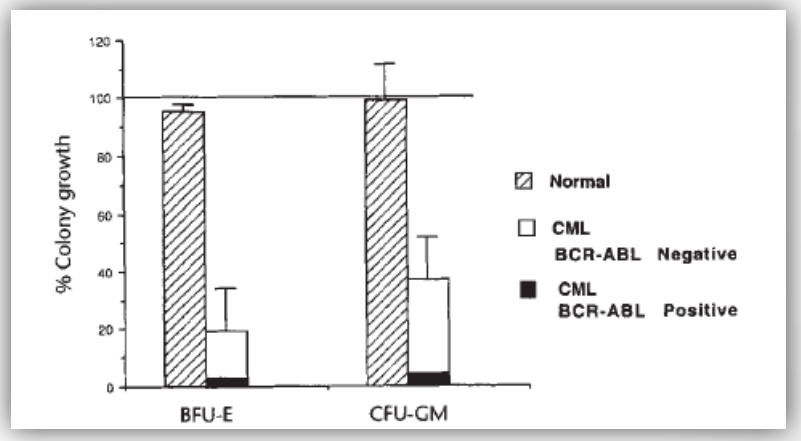
Jabbour EJ, et al., Tyrosine kinase inhibition: a therapeutic target for the management of chronic-phase chronic myeloid leukemia. Expert Rev Anticancer Ther. 2013; 13: 1433-1452.

IMATINIB

Table 1 Profile of inhibition of protein kinases by CGP 57148

Protein kinase	Substrate phosphorylation IC_{50} value (μM)	Cellular tyrosine phosphorylation IC_{50} value (μM)
v-Abl	0.038	0.25
Bcr-Abl	0.025	0.25
c-Abl	0.025	
EGFR-R–ICD	>100	>100
Her-2/neu		>100
Insulin receptor		>100
IGF-1R		>100
PDGF-R		0.3
c-Src	>100	
v-Src		>100
c-Fgr	>100	
c-Lyn	>100	
v-Fms		>100
TPK-IIB	>100	
PKA	>500	
PPK	>100	
PKC α, β1, β2, γ, ε, σ, η, ζ	>100	
Casein kinases - 1 and 2	>100	
cdc2/cyclin	>100	





Druker BJ, Tamura S, Buchdunger E et al., Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells. Nat Med. 1996; 2(5): 561-566.

INDICAZIONI TERAPEUTICHE

4.1 Indicazioni terapeutiche

Glivec è indicato per il trattamento di

- pazienti adulti e pediatrici con leucemia mieloide cronica (LMC) con cromosoma Philadelphia (bcr-abl) positivo (Ph+) di nuova diagnosi, per i quali il trapianto di midollo osseo non è considerato come trattamento di prima linea.
- pazienti adulti e pediatrici con LMC Ph+ in fase cronica dopo il fallimento della terapia con interferone-alfa, o in fase accelerata o in crisi blastica.
- pazienti adulti e pediatrici con leucemia linfoblastica acuta con cromosoma Philadelphia positivo (LLA Ph+) di nuova diagnosi integrato con chemioterapia.
- pazienti adulti con LLA Ph+ recidivante o refrattaria come monoterapia.
- pazienti adulti con malattie mielodisplastiche/mieloproliferative (MDS/MPD) associate a riarrangiamenti del gene del recettore per il fattore di crescita di origine piastrinica (PDGFR).
- pazienti adulti con sindrome ipereosinofila avanzata (HES) e/o con leucemia eosinofila cronica (LEC) con riarrangiamento FIP1L1-PDGFRα.

L'effetto di Glivec sull'esito del trapianto di midollo osseo non è stato determinato.

Glivec è indicato per

- il trattamento di pazienti adulti con tumori stromali del tratto gastro-intestinale (GIST) maligni non operabili e/o metastatici positivi al Kit (CD 117).
- il trattamento adiuvante di pazienti adulti con un significativo rischio di recidiva dopo resezione di GIST positivi al Kit (CD 117). I pazienti con un rischio di recidiva basso o molto basso non dovrebbero ricevere il trattamento adiuvante.
- il trattamento di pazienti adulti con dermatofibrosarcoma protuberans (DFSP) non resecabile e pazienti adulti con DFSP recidivante e/o metastatico non elegibili per la chirurgia.

OBIETTIVI TERAPEUTICI

Table 1. European Leukemia Net criteria detailing minimum required response therapy from initiation, with definitions of response†.

Response	Criteria		
Complete heamatologic response (CHR)	Normalization of peripheral blood and resolution of splenomegaly		
Minimal cytogenetic response	>65–95% Ph+ in bone marrow		
Minor cytogenetic response	>35–66% Ph+ in bone marrow		
Partial cytogenetic response	0–35% Ph+ in bone marrow		
Complete cytogenetic response (CCyR)	0% Ph+ in bone marrow		
Major molecular response (MMR)	3 log reduction in *BCR-ABL1* relative to control		
Complete molecular response (CMR)	Undetectable *BCR-ABL1* transcripts by qRT-PCR		
	Optimal	Warning	
3 months	*BCR-ABL1* ≤10% ±Ph+ <35%	*BCR-ABL1* >10% ±Ph+ 36–95%	No CHR, and/or Ph+ >95%
6 months	*BCR-ABL1* <1% ±Ph+ 0	*BCR-ABL1* >10% ±Ph+ 1–35%	*BCR-ABL1* >10% and/or Ph+ >35%
12 months	*BCR-ABL1* ≤0.1%	*BCR-ABL1* >0.1–1%	*BCR-ABL1* >1% and/or Ph+ >0
Thereafter	*BCR-ABL1* ≤0.1%	Confirmed clonal abnormalities, Ph	Loss of CHR; loss of CCyR; confirmed loss of MMR

†Data taken from [11].
BCR-ABL1: Quantitative PCR assessment of *BCR-ABL1*:ABL1 (or other housekeeping gene) on the International Scale; CCyR: Complete cytogenetic response; CHR: Complete hematologic response; CMR: Complete molecular response; MMR: Major molecular response; Ph+: Philadelphia chromosome positive.

CP CML patients

Imatinib (400 mg/daily)

- 60% highly effective
- 20% do not achieve or maintain optimal response
- 20 % unable to tolerate therapy

(*Hughes T, White D. Which TKI? An embarrassment of riches for chronic myeloid leukemia patients. Hematology Am Soc Hematol Educ Program. 2013; 2013: 168-175*)

Horne GA, Kinstrie R, Copland M. Novel drug therapies in myeloid leukemia. Pharm Pat Anal. 2015; 4: 187-205.

Pharmacogenetics and IMATINIB

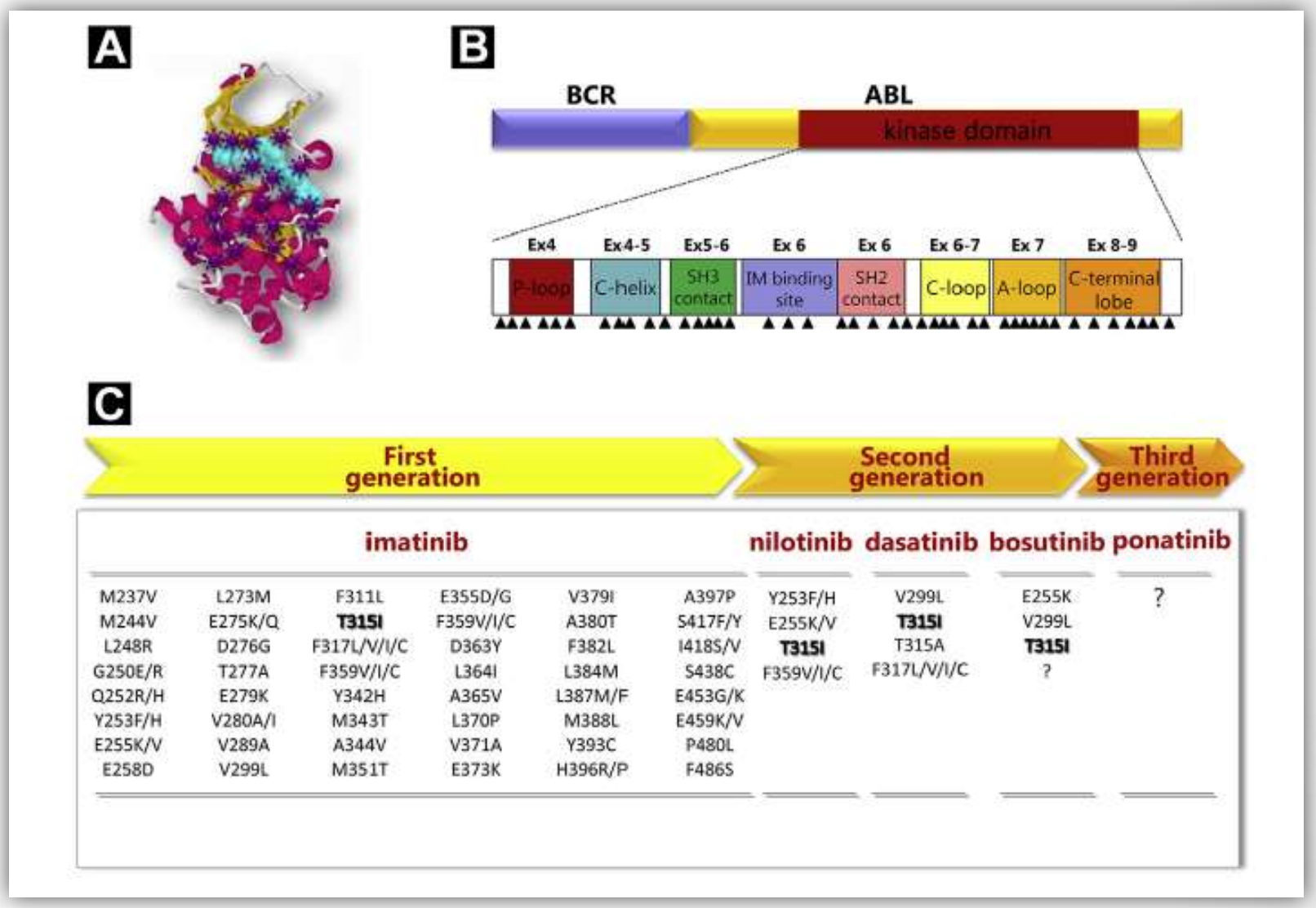
CYP3A isoforms: mainly involved in the metabolic *clearance* of imatinib → N-desmethyl-imatinib (CPG74588) → approximately 20% of plasma levels of the parent drug and 3–4 times less toxic → drug-drug interactions and genetic variability

ATP-binding cassette (ABC) transporters (ABCB1 e ABCG2): involved in the intestinal absorption of the drug and renal elimination as well as cellular extrusion of the drug (imatinib resistance)

SLC22A1 (hOCT1): involved in the cellular uptake of imatinib

Polillo M, Galimberti S et al., Pharmacogenetics of BCR/ABL Inhibitors in Chronic Myeloid Leukemia. Int J Mol Sci. 2015 ; 16: 22811-22829.

Pharmacogenetics and IMATINIB



imatinib						nilotinib	dasatinib	bosutinib	ponatinib
M237V	L273M	F311L	E355D/G	V379I	A397P	Y253F/H	V299L	E255K	?
M244V	E275K/Q	**T315I**	F359V/I/C	A380T	S417F/Y	E255K/V	**T315I**	V299L	
L248R	D276G	F317L/V/I/C	D363Y	F382L	I418S/V	**T315I**	T315A	**T315I**	
G250E/R	T277A	F359V/I/C	L364I	L384M	S438C	F359V/I/C	F317L/V/I/C	?	
Q252R/H	E279K	Y342H	A365V	L387M/F	E453G/K				
Y253F/H	V280A/I	M343T	L370P	M388L	E459K/V				
E255K/V	V289A	A344V	V371A	Y393C	P480L				
E258D	V299L	M351T	E373K	H396R/P	F486S				

Soverini S, de Benedittis C et al., Mutations in the BCR-ABL1 Kinase Domain and Elsewhere in Chronic Myeloid Leukemia. Clin Lymphoma Myeloma Leuk; 15 Suppl: S120-S128.

SECOND GENERATION TKIs

Active Substance	Name	Pharmaceutical Company	EMA Approval
Imatinib	Glivec	Novartis	2001*
Nilotinib	Tasigna	Novartis	2009
Dasatinib	Sprycel	Bristol-Meyer Squibb	2009

- More selective inhibition of ABL (lower PDGFR/cKIT)
- Inactive conformation of BCR/ABL
- 30-50 fold incresead binding affinity than imatinib

- Increased Pharmacological Potency

- Dual ABL/SRC inhibitor
- Active and inactive conformation of BCR/ABL
- 325 times more potent than imatinib

Horne GA, Kinstrie R, Copland M. Novel drug therapies in myeloid leukemia. Pharm Pat Anal. 2015; 4: 187-205.

THIRD GENERATION TKIs

Active Substance	Name	Pharmaceutical Company	EMA Approval
Imatinib	Glivec	Novartis	2001*
Nilotinib	Tasigna	Novartis	2009
Dasatinib	Sprycel	Bristol-Meyer Squibb	2009
Bosutinib	Bosulif	Pfizer Ltd	2013
Ponatinib	Iclusig	Ariad Pharma Ltd	2013

- Increased Pharmacological Potency

- Dual ABL/SRC inhibitor

- Active on the T351I mutation

Hughes T, White D. Which TKI? An embarrassment of riches for chronic myeloid leukemia patients. Hematology Am Soc Hematol Educ Program. 2013; 2013: 168-175

European LeukemiaNet Reccomendations for the treatment of CML: CP

Table 7. Chronic phase treatment recommendations for first, second, and subsequent lines of treatment

First line
Imatinib or nilotinib or dasatinib
HLA type patients and siblings only in case of baseline warnings (high risk, major route CCA/Ph+)
Second line, intolerance to the first TKI
Anyone of the other TKIs approved first line (imatinib, nilotinib, dasatinib)
Second line, failure of imatinib first line
Dasatinib or nilotinib or bosutinib or ponatinib
HLA type patients and siblings
Second line, failure of nilotinib first line
Dasatinib or bosutinib or ponatinib
HLA type patients and siblings; search for an unrelated stem cell donor; consider alloSCT
Second line, failure of dasatinib first line
Nilotinib or bosutinib or ponatinib
HLA type patients and siblings; search for an unrelated stem cell donor; consider alloSCT
Third line, failure of and/or intolerance to 2 TKIs
Anyone of the remaining TKIs; alloSCT recommended in all eligible patients
Any line, T315I mutation
Ponatinib
HLA type patients and siblings; search for an unrelated stem cell donor; consider alloSCT

Baccarani M, Deininger MW et al., LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood. 2013; 122: 872-884.

CHRONIC PHASE: FIRST line of TREATMENTS

Table 1. Comparison of the efficacy profiles (% achievement) of nilotinib,[13] dasatinib,[19] and bosutinib[45] in the 3 registration phase 3 studies compared with imatinib

End point	Nil(300)	IM	DAS	IM	BOS	IM
CCyR by 12 mo	80	65	85	73	70	68
CCyR by 24 mo	87	77	86	82	87	81
MMR by 24 mo	53	27	46	28	41	27
MMR by 24 mo	69	44	64	46	61	50
MR4.5 by 24 mo	23	10	17	8	25	17
Transformation	2.6	6.7	3.5	5.8	2	4
Death	3.7	6	6	5	2	5
Overall survival	95.1*	94*	95.3	95.2†	99‡	95‡

Nil(300) indicates nilotinib 300 mg; IM, imatinib; DAS, dasatinib; and BOS, bosutinib.
*Median follow-up was 36 months.
†Median follow-up was 24 months.
‡Median follow-up was 18 months.

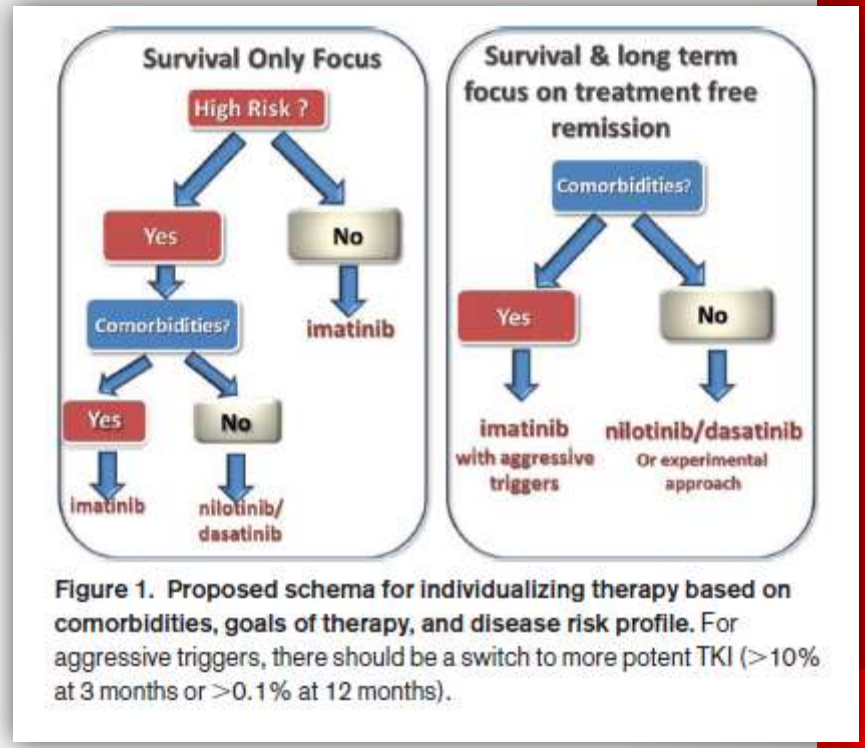


Figure 1. Proposed schema for individualizing therapy based on comorbidities, goals of therapy, and disease risk profile. For aggressive triggers, there should be a switch to more potent TKI (>10% at 3 months or >0.1% at 12 months).

Hughes T, White D. Which TKI? An embarrassment of riches for chronic myeloid leukemia patients. Hematology Am Soc Hematol Educ Program. 2013;2013:168-75.

European LeukemiaNet Reccomendations for the treatment of CML: CP

Table 7. Chronic phase treatment recommendations for first, second, and subsequent lines of treatment

First line
Imatinib or nilotinib or dasatinib
HLA type patients and siblings only in case of baseline warnings (high risk, major route CCA/Ph+)
Second line, intolerance to the first TKI
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Second line, failure of imatinib first line
Dasatinib or nilotinib or bosutinib or ponatinib
HLA type patients and siblings
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Dasatinib or bosutinib or ponatinib
HLA type patients and siblings; search for an unrelated stem cell donor; consider alloSCT
Second line, failure of dasatinib first line
Nilotinib or bosutinib or ponatinib
HLA type patients and siblings; search for an unrelated stem cell donor; consider alloSCT
Third line, failure of and/or intolerance to 2 TKIs
Anyone of the remaining TKIs; alloSCT recommended in all eligible patients
Any line, T315I mutation
Ponatinib
HLA type patients and siblings; search for an unrelated stem cell donor; consider alloSCT

Table 5 Provisional list of the more critical BCR-ABL1 mutations

BCR-ABL1 mutation	Poorly sensitive to	Resistant to
G250E	Bosutinib	
Q252H	Dasatinib	
Y253H	Nilotinib	
E255K/V	Bosutinib, dasatinib, nilotinib, ponatinib	
T3151		Bosutinib, dasatinib, nilotinib
F317L	Dasatinib	
F355V	Nilotinib	
H396R	Ponatinib	

The assessment of sensitivity was based on in-vitro data (the inhibitory concentration 50 %) and on clinical data. All these mutations, as well as many other mutations, are poorly sensitive or resistant also to imatinib

Baccarani M, Castagnetti F, et al. A review of the European LeukemiaNet recommendations for the management of CML. Ann Hematol. 2015; 94: S141-S147.

Baccarani M, Deininger MW et al., LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood. 2013; 122: 872-884.

European LeukemiaNet Reccomendations for the treatment of CML: AP & BP

Table 8. Treatment strategy recommendations for CML in AP or BP

AP and BP in newly diagnosed, TKI-naïve patients	Imatinib 400 mg twice daily or dasatinib 70 mg twice daily or 140 mg once daily Stem cell donor search. Then, alloSCT is recommended for all BP patients and for the AP patients who do not achieve an optimal response. Chemotherapy may be required before alloSCT, to control the disease.
AP and BP as a progression from CP in TKI-pretreated patients	Anyone of the TKIs that were not used before progression (ponatinib in case of T315I mutation), then alloSCT in all patients. Chemotherapy is frequently required to make patients eligible for alloSCT.

Baccarani M, Deininger MW et al., LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood. 2013; 122: 872-884.

Medicines under additional monitoring

AIFA AGENZIA ITALIANA DEL FARMACO

REGISTRO DEI FARMACI ONCOLOGICI SOTTOPOSTI A MONITORAGGIO

Eleggibili solo pazienti di età ≥ 18 anni

CODICE PAZIENTE	CENTRO	INIZ. PAZ.	DATA REGISTRAZIONE	DATA DI NASCITA

I campi contrassegnati dalla lettera (E) sono determinanti per l'eleggibilità.
I campi contrassegnati con * sono obbligatori.

DIAGNOSI

INDICAZIONI TERAPEUTICHE
- SPRYCEL -

Trattamento di adulti con leucemia mieloide cronica (LMC), con cromosoma Philadelphia positivo di nuova diagnosi in fase cronica.

AIFA AGENZIA ITALIANA DEL FARMACO

REGISTRO DEI FARMACI ONCOLOGICI SOTTOPOSTI A MONITORAGGIO

eleggibili solo pazienti di età ≥ 18 anni

DIAGNOSI

INDICAZIONI TERAPEUTICHE
- TASIGNA -

Trattamento di adulti con leucemia mieloide cronica (LMC), con cromosoma Philadelphia positivo di nuova diagnosi in fase cronica.

I campi contrassegnati dalla lettera (E) sono determinanti per l'eleggibilità.
I campi contrassegnati con * sono obbligatori.