EVOLUZIONE DELLA TERAPIA IN ONCOEMATOLOGIA: DALLA CHEMIOTERAPIA ALLA TERAPIA TARGET

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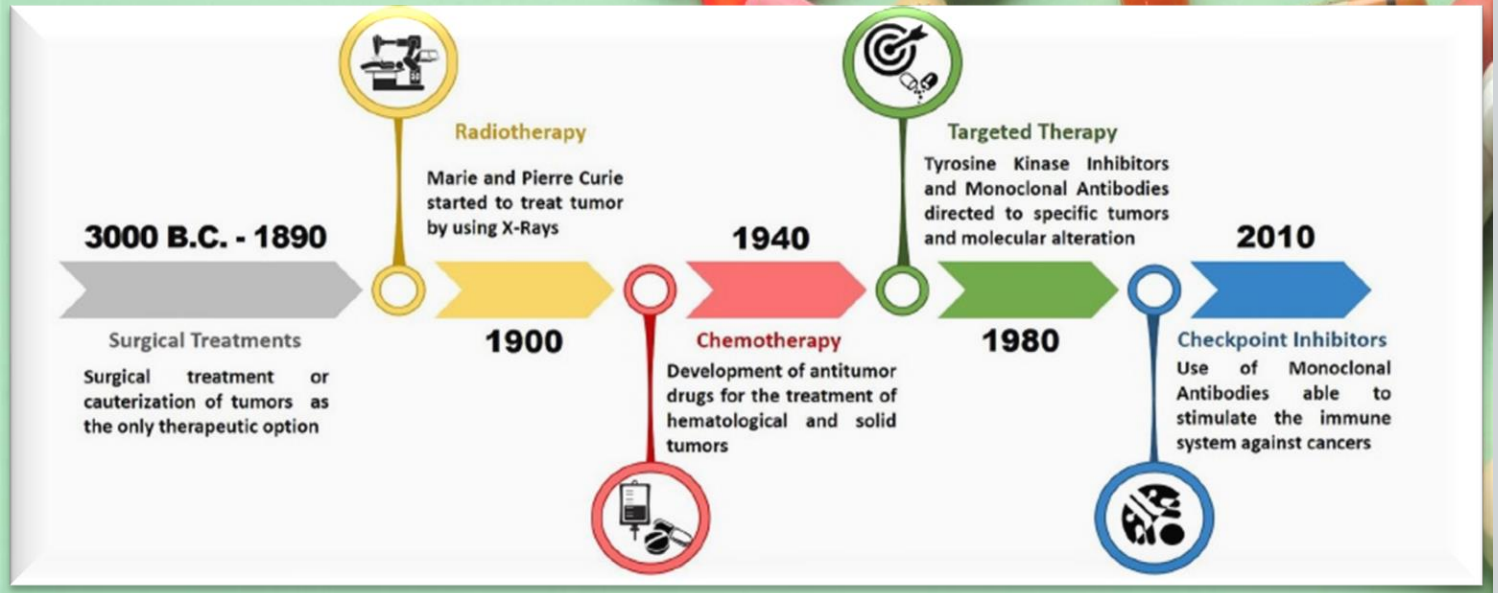


Agenda

- ❑Evolution of the therapy in oncohematology
- ❑BCR-ABL1 as TKIs and asciminib target in CML
- ❑PML-RARalpha as target of ATRA therapy in APL
- ❑JAK2 mutated as target of ruxolitinib in MPNs
- ❑FLT3-ITD and IDH2 mutated as target of target therapy in AML

Falzone et al., Frontiers in Pharmacology 2018

TERAPIA TRADIZIONALE

FARMACI CHEMIOTERAPICI
In grado di interferire con la replicazione cellulare

Contro le cellule tumorali

Contro i tessuti sani

NUOVI BERSAGLI

Ridotta tossicità
Maggiore specificità antitumorale
Terapia individualizzata

CELLULE NEOPLASTICA

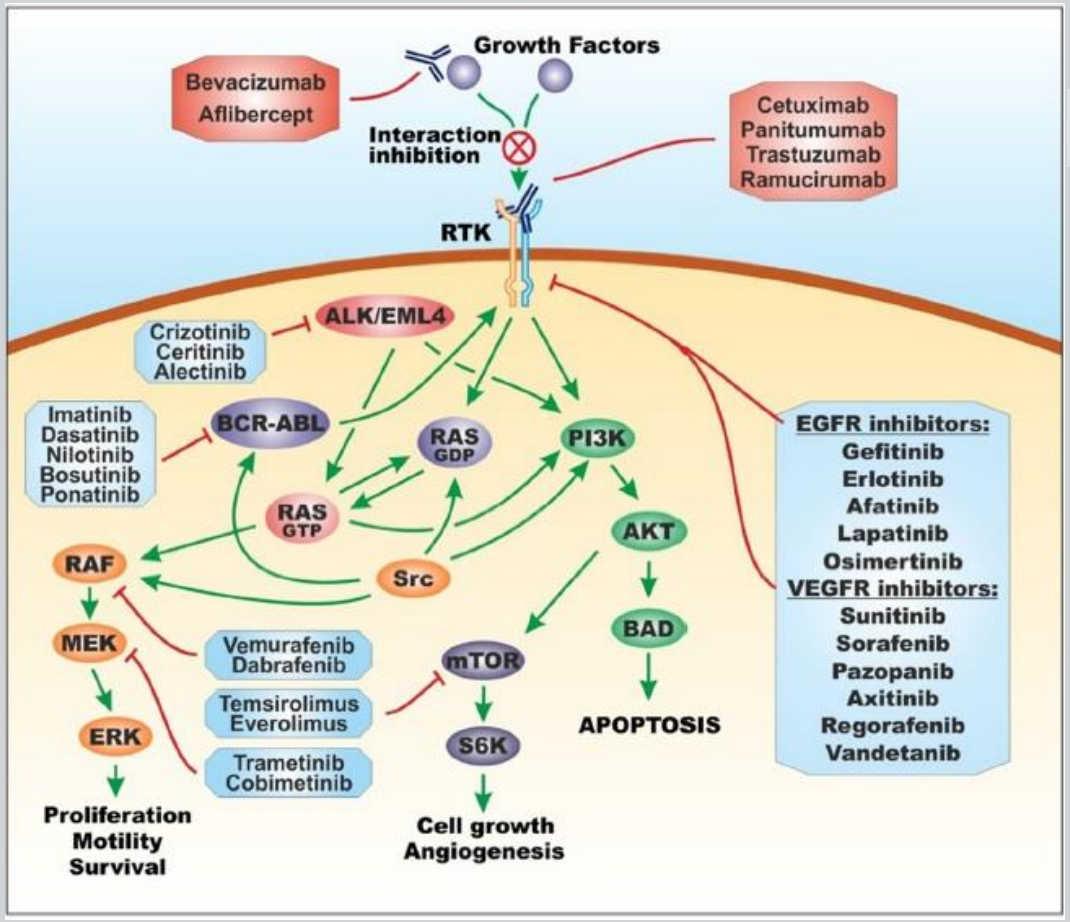
CRESCITA RESISTENZA DIFFUSIONE

I progressi della biologia cellulare e molecolare hanno identificato **nuovi bersagli terapeutici**

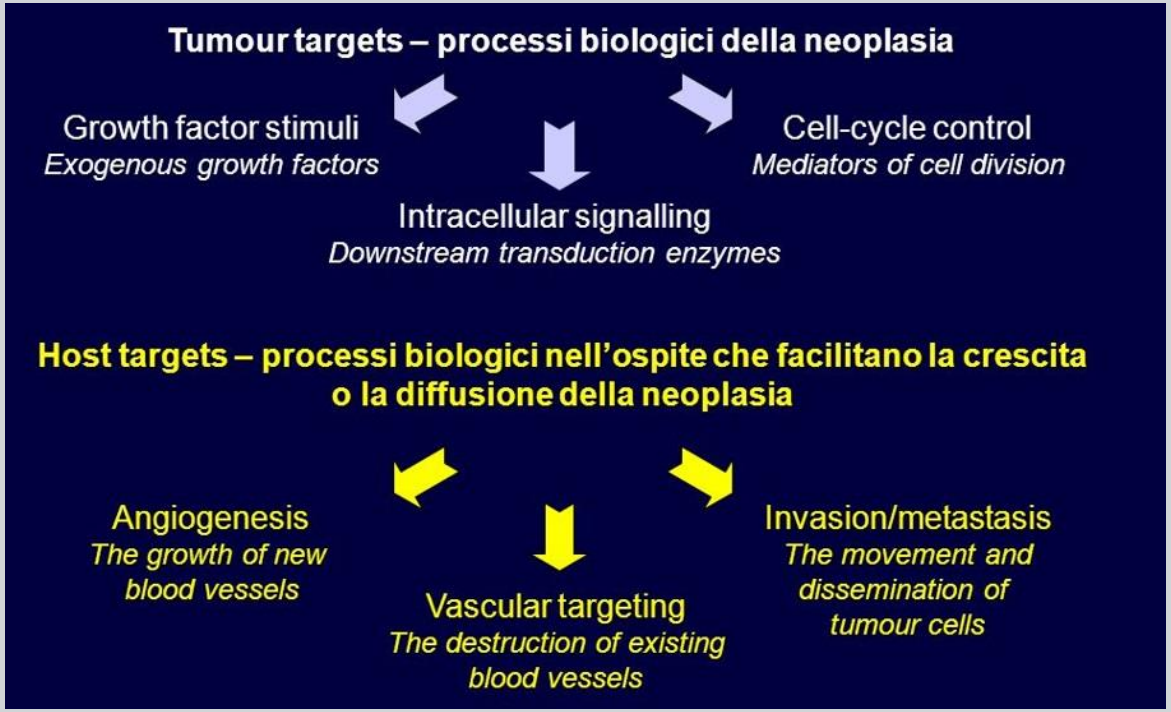
TERAPIA IN ASSOCIAZIONE:

- ✓ ↑ dell'effetto citotossico massimale e ↓ della tossicità
- ✓ possibilità di uccidere cellule con caratteristiche diverse in popolazioni tumorali eterogenee
- ✓ ↓ della probabilità di sviluppo di cloni resistenti

Molecular targets of targeted therapy

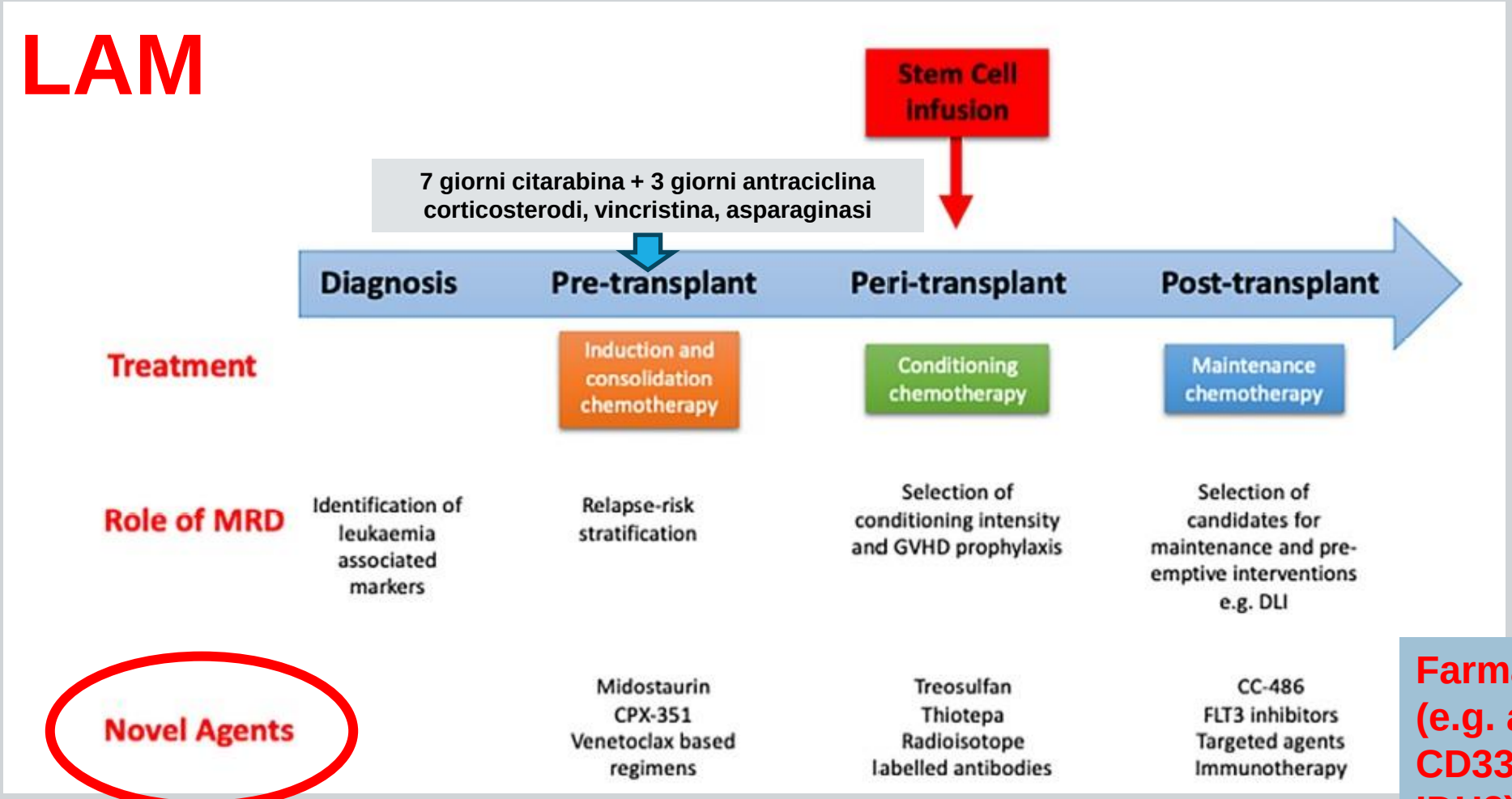


Treatments affecting specific molecular targets



Falzone et al., Frontiers in Pharmacology 2018

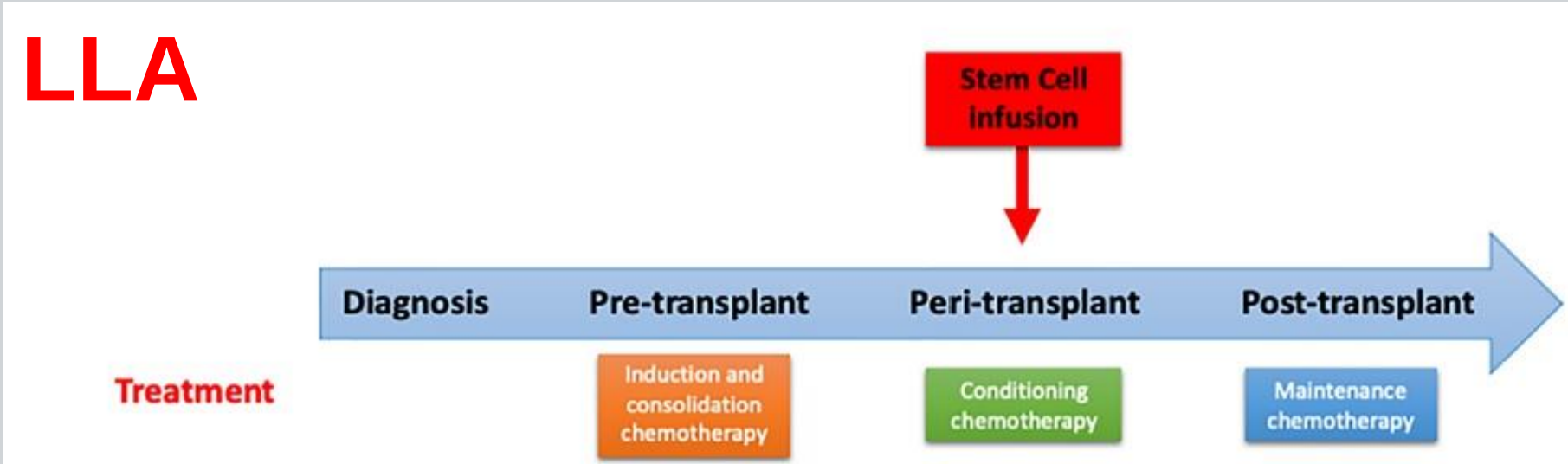
Leucemia acuta: terapia nell'adulto



Farmaci target-specifici (e.g. anti-FLT3, anti-CD33, anti-IDH1, anti-IDH2).

Leucemia acuta: terapia nell'adulto

LLA

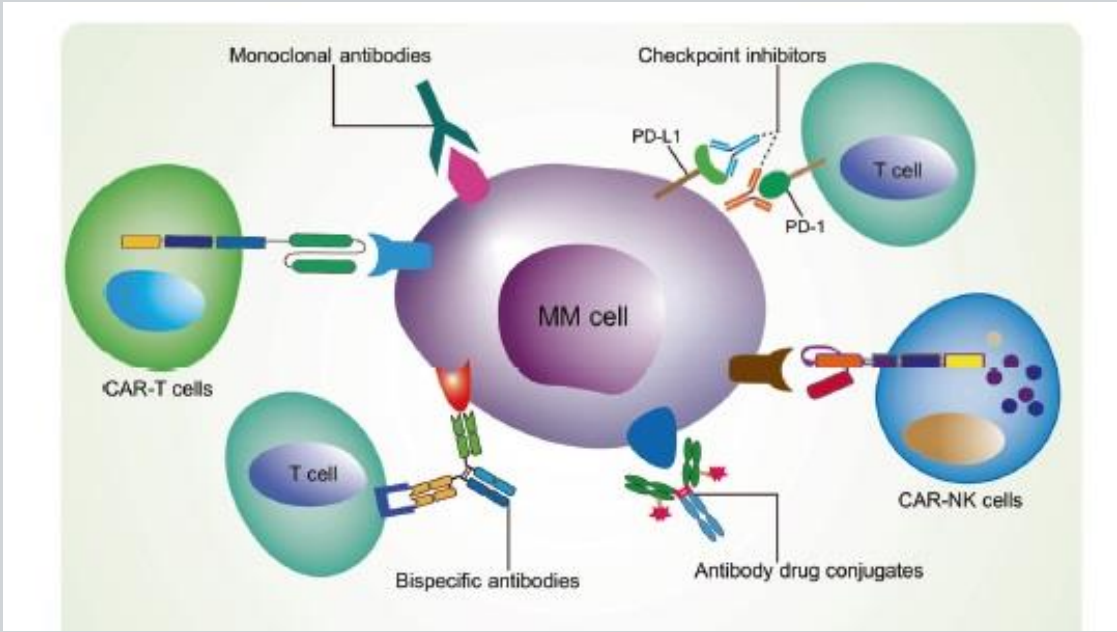


Mieloma Multiplo: terapia nell'adulto

Farmaci che targettano il clone neoplastico e il microambiente midollare:

1. Cortisonici, alchilanti
2. **Immunomodulatori (IMiDs) (Lenalidomide** e **Pomalidomide)**.
3. **Inibitori del proteasoma (PIs) (Bortezomib)**
4. **Ab monoclonali**, es. daratumumab **anti-CD38**, elotuzumab (**anti-SLAMF7**), venetoclax (inibitore di **BCL-2**), **CAR-T**.

Targeted Immunotherapy



L. Xu et al., Cell Death Discovery (2024)

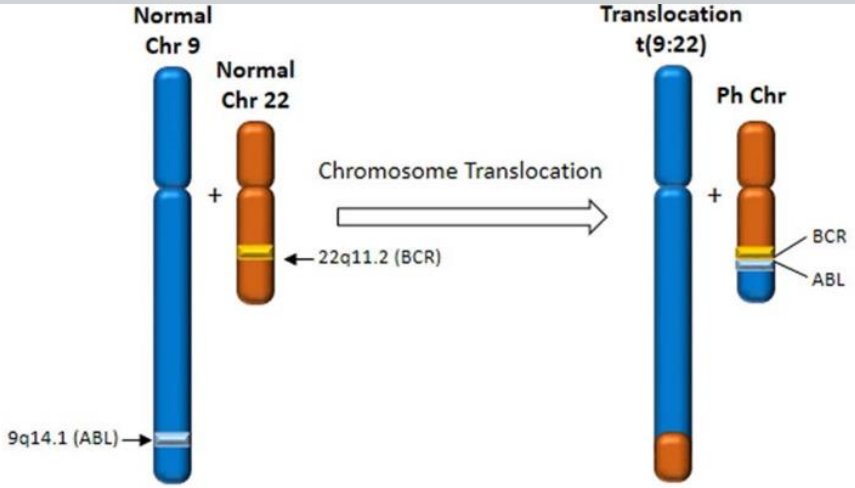
BCR::ABL1 as target of TKIs therapy and asciminib

CHRONIC MYELOID LEUKEMIA

CHRONIC MYELOID LEUKEMIA (CML)

- Philadelphia+ Chronic Myeloid Leukemia (Ph+ CML) is an hematologic malignancy arising from the chromosomal alteration t(9;22).

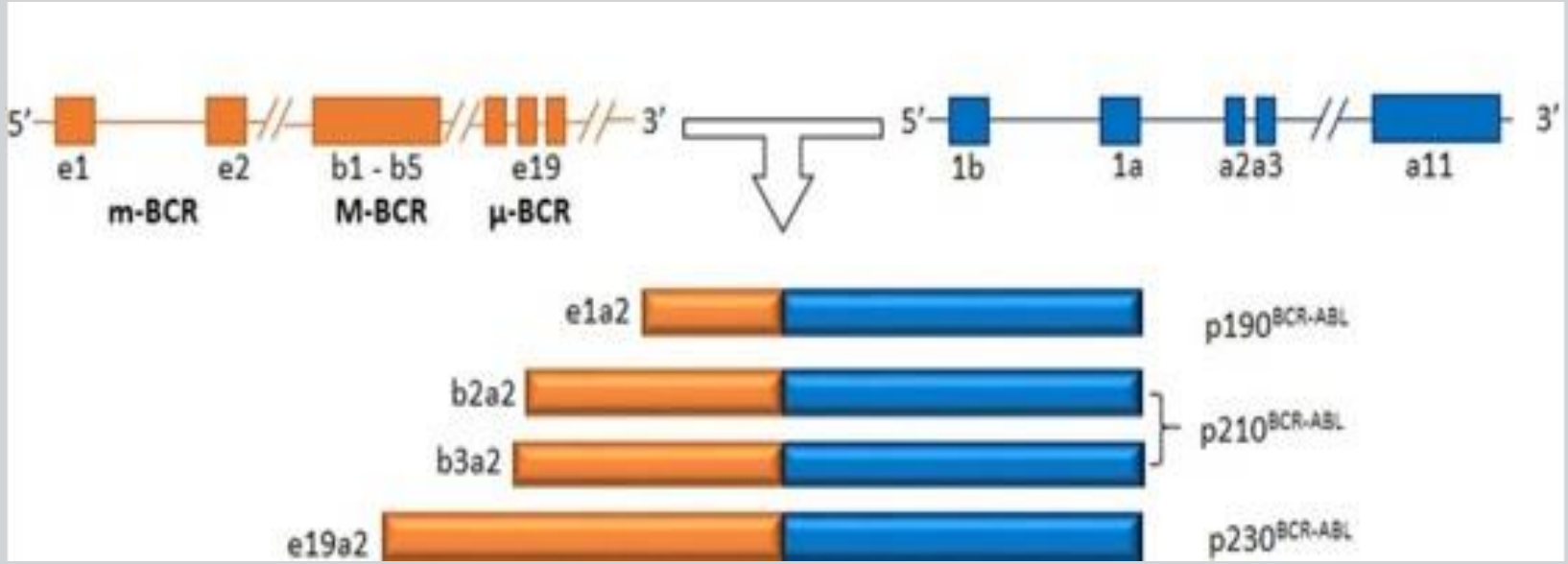
- The fusion gene BCR::ABL1 is generated by this translocation and it is the hallmark of Ph+ CML.



- ❑ **ABL: Tyrosyn-kinase with enzimatic activity.**
- ❑ **BCR: serin/treonyn kinase with a key role in the signal transduction.**

t(9;22)(q34;q11.2)

CHIMERIC PROTEIN ISOFORMS

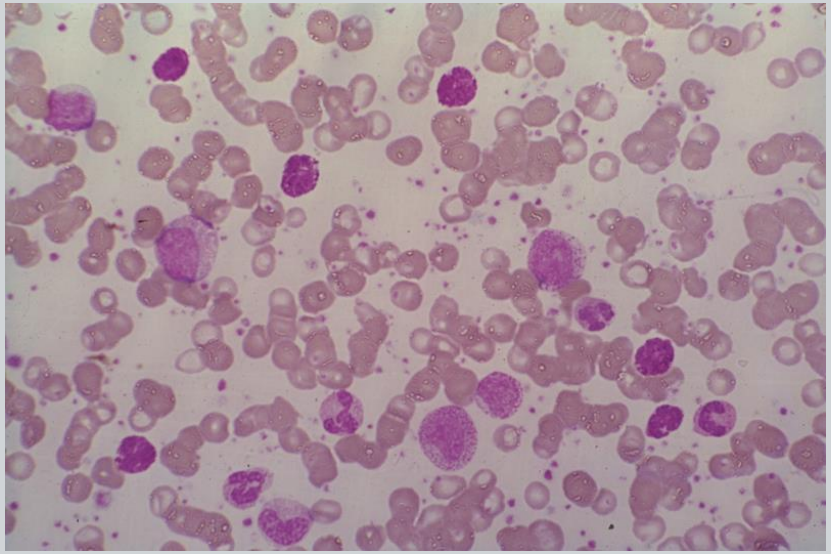


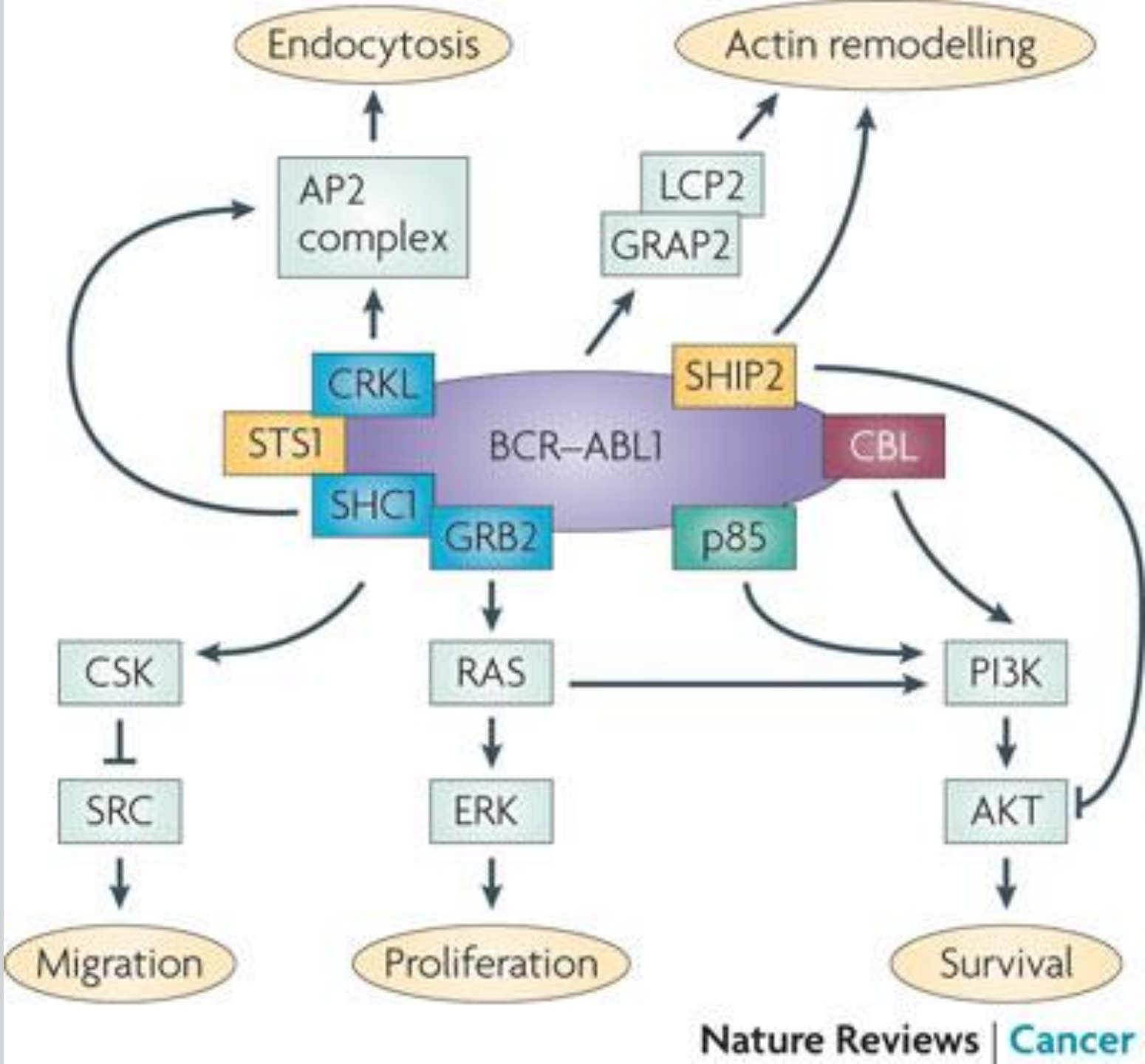
p190 (LAL)

p210 (CML, raramente LAL)

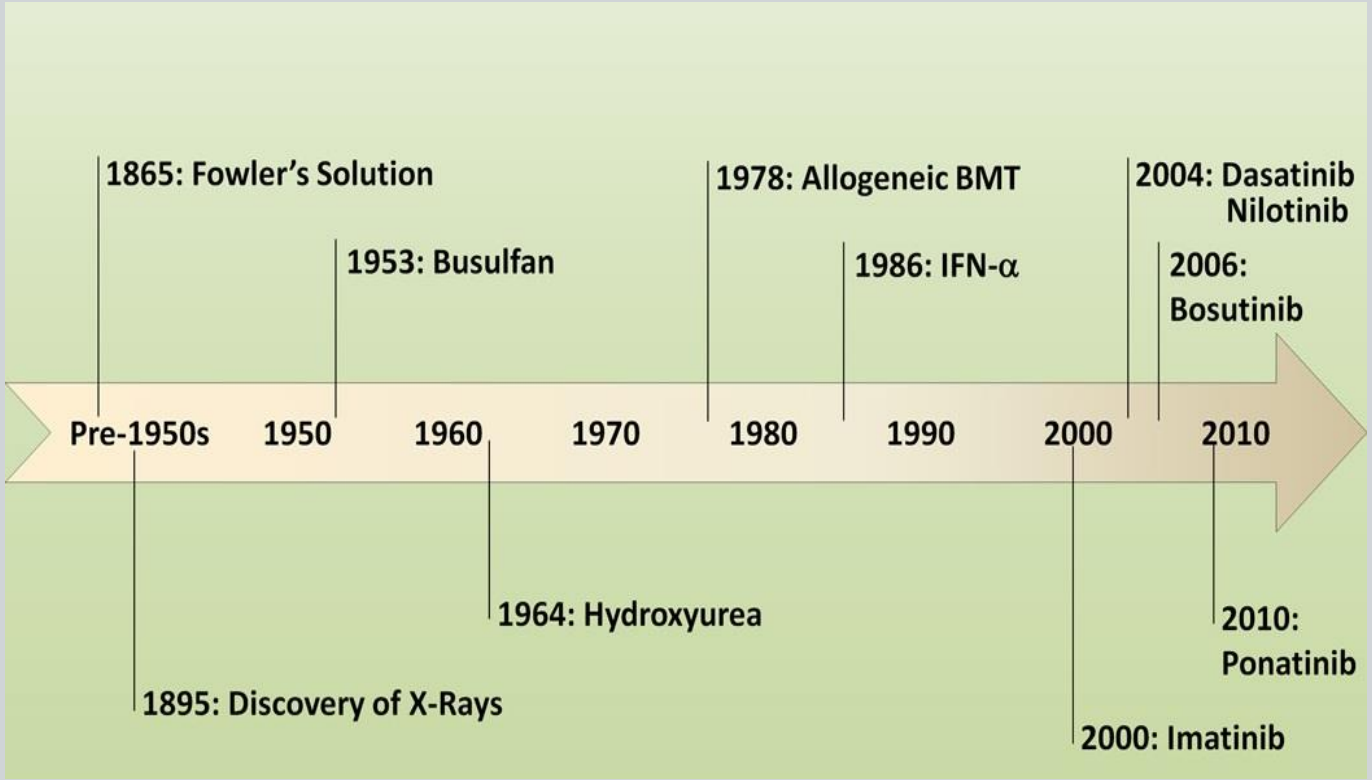
p230 (CML)

PATHWAY ACTIVATED BY BCR-ABL1 EXPRESSION





TIMELINE OF THERAPY FOR CML



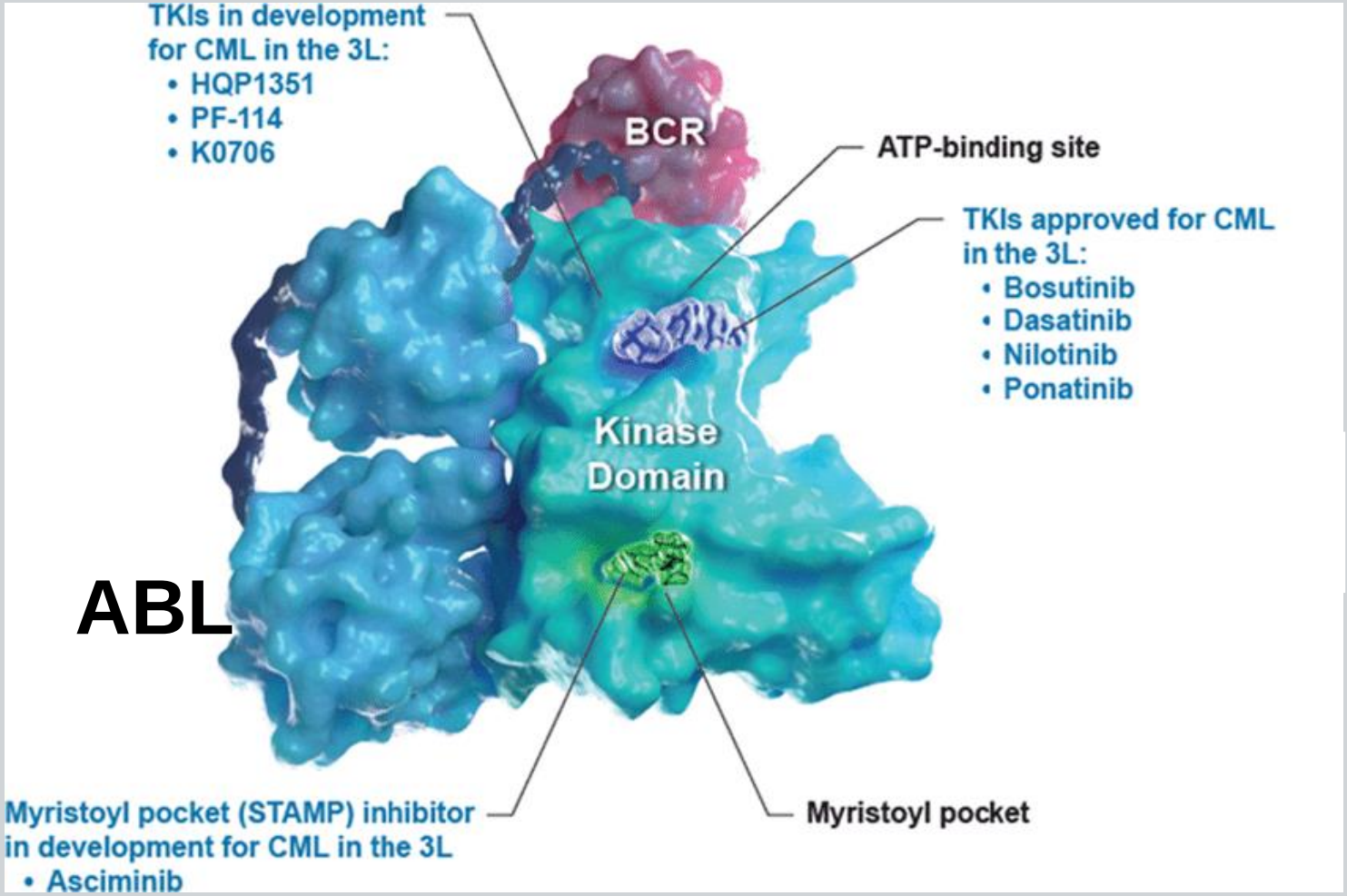
1845 recognition of leukemia as a disease entity
1865 first treatment with 1% arsenic solution
1895 discovery of x-irradiation
1946 nitrogen mustard - first effective chemotherapy
1953 busulfan
1960 hydroxyurea
1978 autografts for CML
1982 routine use of allografts for CML
1983 interferon
1990 donor lymphocyte infusions (DLI)
1999 Imatinib
2004 New TKIs

NEW TYROSINE KINASE INIBITHOR (TKIs)

Imatinib is proof of principle that rationally designed, molecularly targeted therapy works. Imatinib represents a paradigm shift in cancer drug development.

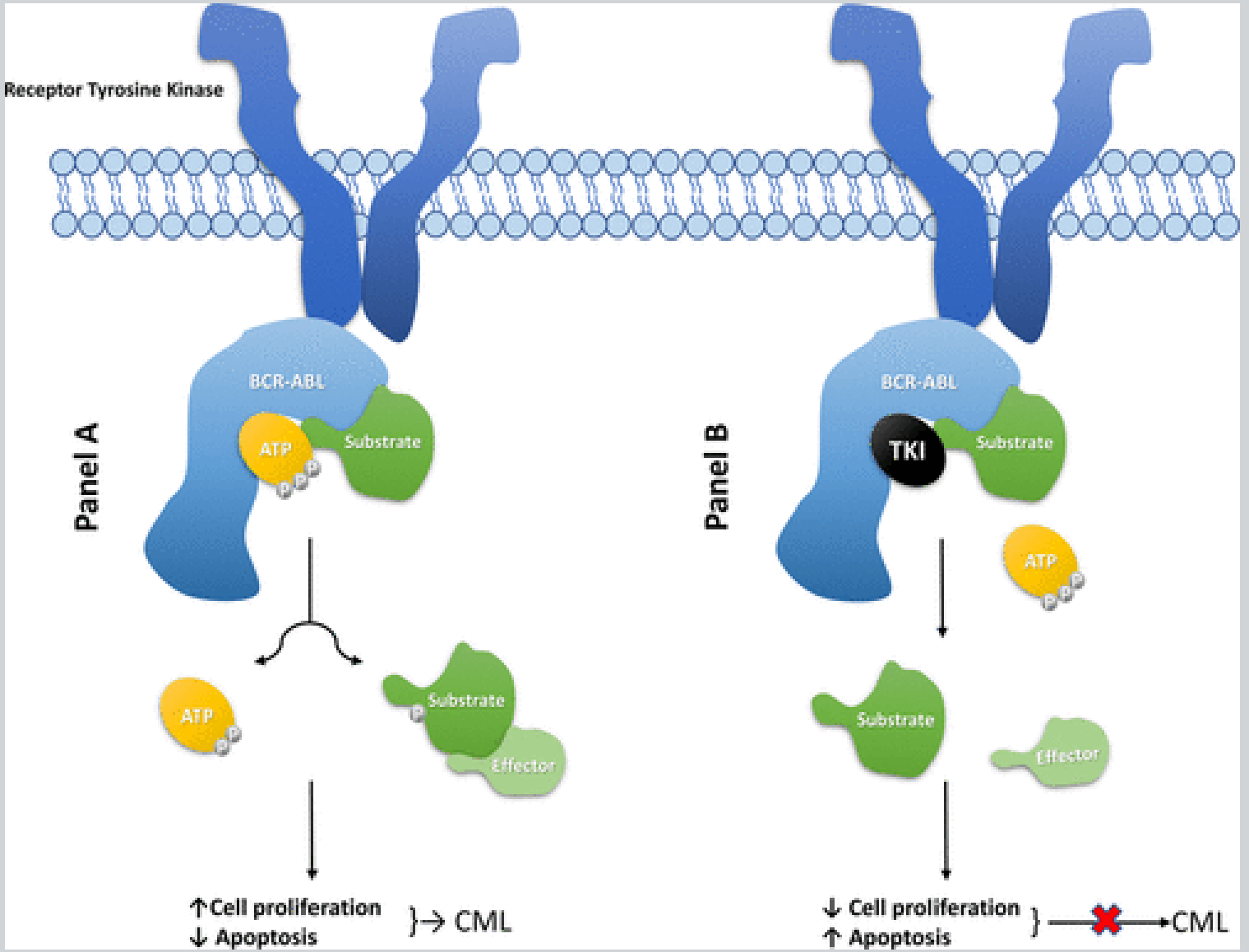
(*Deininiger et al 2005*)

TKIs selectively targeted against BCR::ABL1 protein

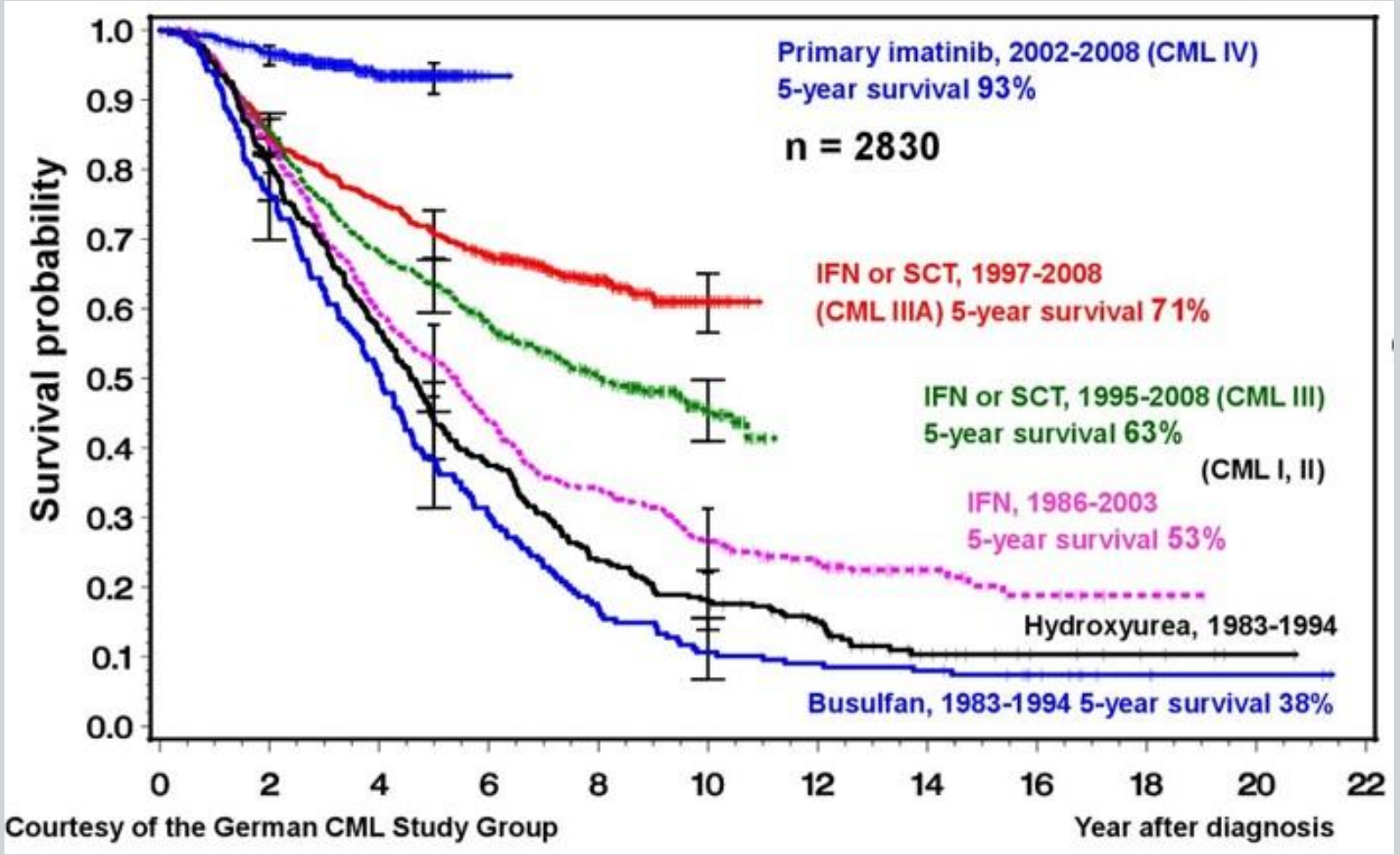


Ph+CML=BCR-ABL1 rearrangements=TKIs

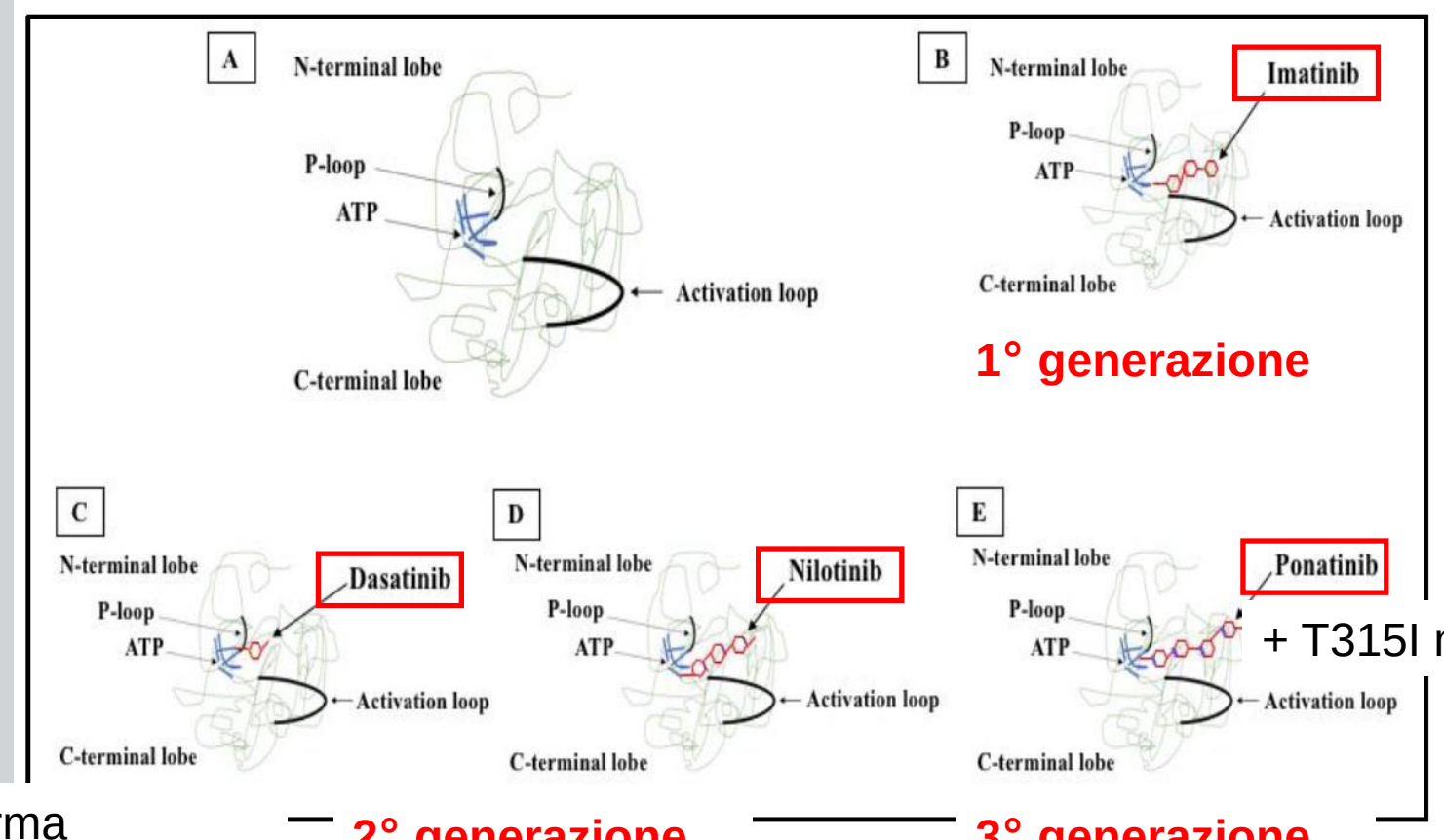
TKIs selectively targeted against BCR::ABL1 protein



SURVIVAL WITH CML1983-2008



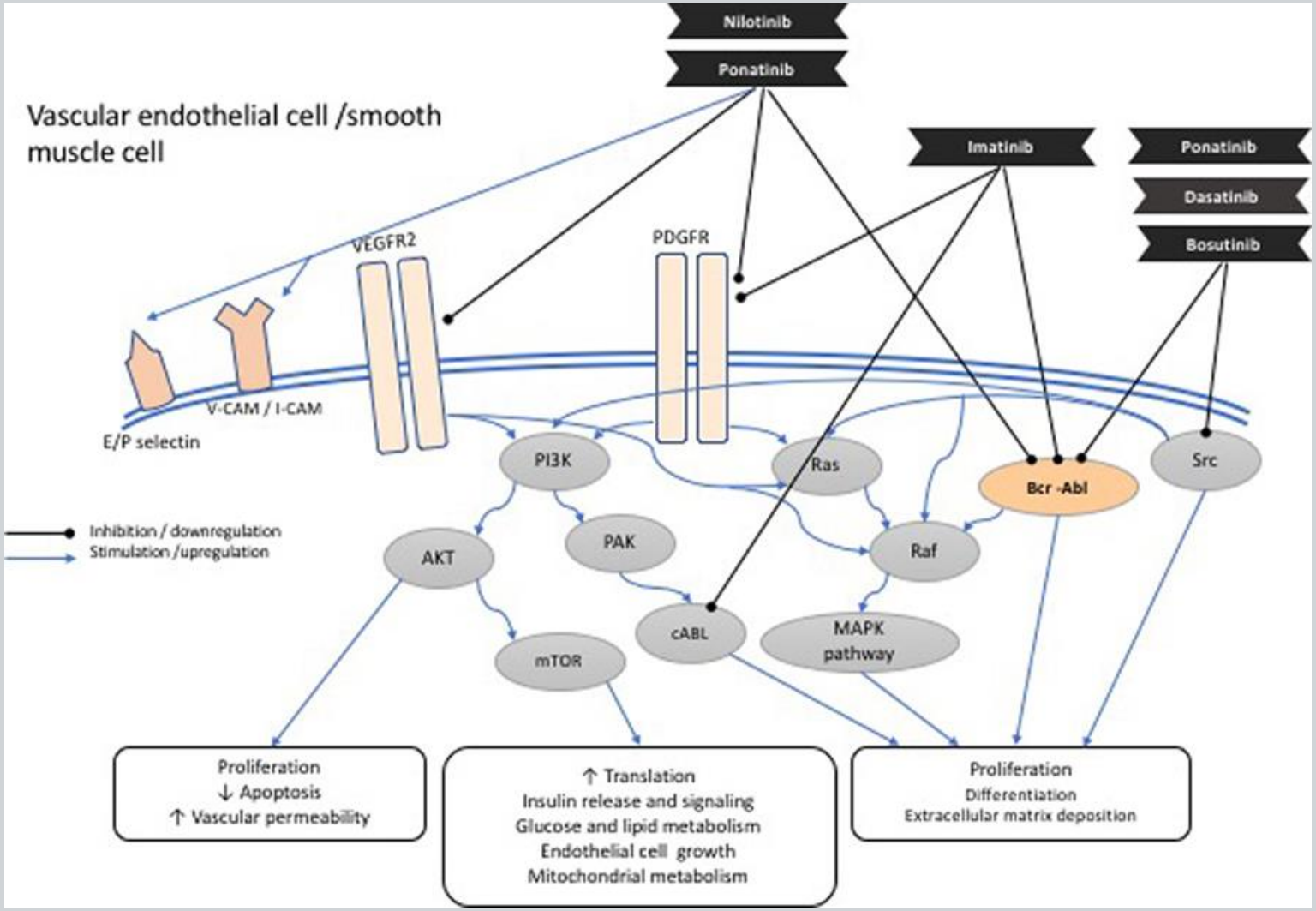
Generations of TKIs



Forma attiva/inattiva della chinasi

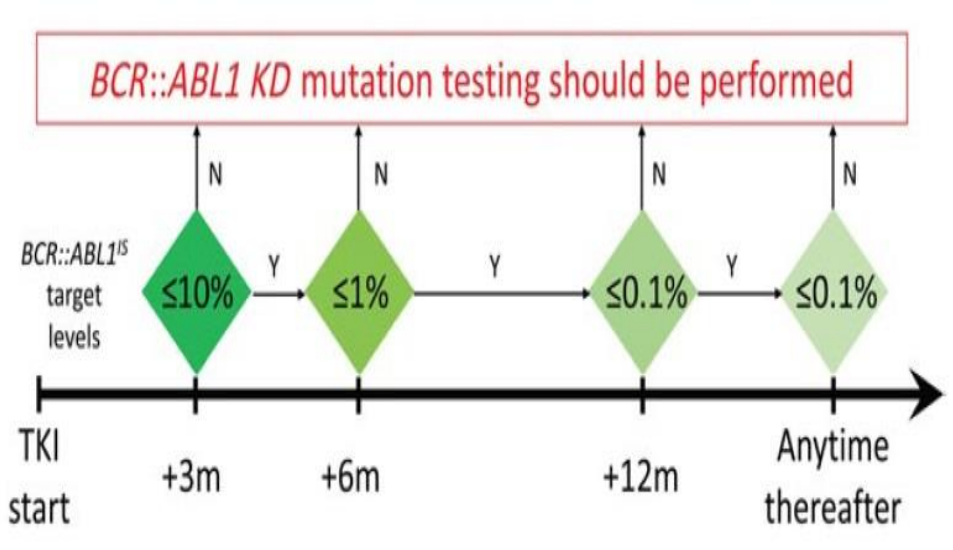
Several TKIs were developed to target the ATP binding site of the kinase domain, thereby preventing phosphorylation of the target protein and subsequent signaling events

TKIs: mechanisms of action



TKIs and MRD

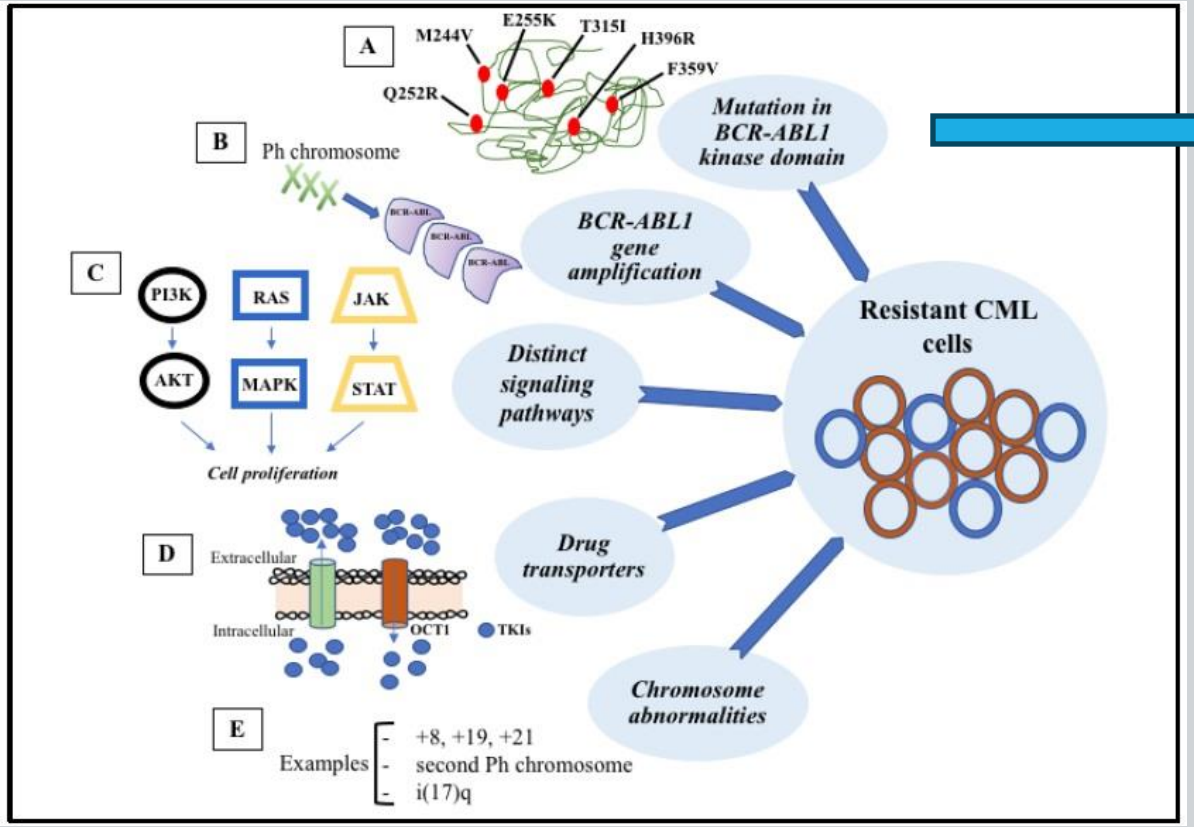
The key goal of the TKIs treatment is to achieve a Minimal Residual Disease

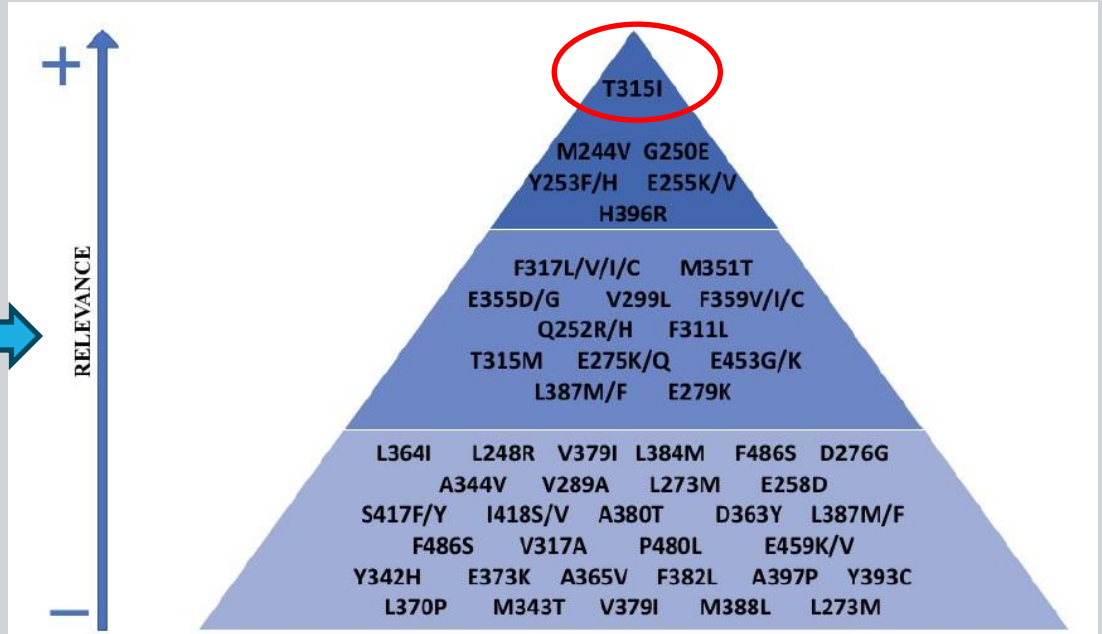


	TIME AFTER START OF TREATMENT			
BCR-ABL1 (IS)	3 months	6 months	12 months[b]	More than 15 months
>10%[a]	YELLOW	RED		
>1%-10%	GREEN		YELLOW	RED
≤1%	GREEN			

Color Code	Concern	Treatment Team Considerations	Potential Decisions About Treatment
RED	TKI-resistant disease	Evaluate patient compliance and drug interactions Consider mutational analysis	Switch to alternate TKI Evaluate for allogeneic HCT
YELLOW	Possible TKI resistance	Evaluate patient compliance and drug interactions Consider mutational analysis Consider bone marrow cytogenetic testing to assess for MCyR at 3 months or CCyR at 12 months	Switch to alternate TKI ***OR*** Continue same TKI (other than imatinib)[c] ***OR*** Dose escalation of imatinib (to a max of 800 mg) ***AND*** Consider evaluation for allogeneic HCT
GREEN	TKI-sensitive disease	Monitor response Monitor and manage side effects as needed	Continue same TKI

Resistence to TKIs





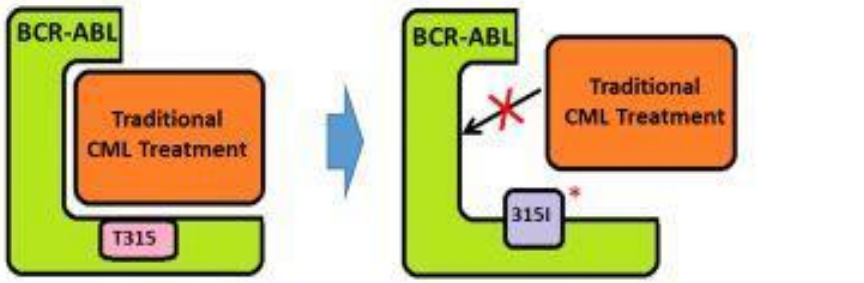
Summary of BCR-ABL1 mutation and preferred TKI

Mutation	Preferred agents
F317L/V/I/C	Nilotinib, bosutinib, ponatinib, or asciminib
T315A	Nilotinib, bosutinib, ponatinib, or asciminib
V299L	Nilotinib, ponatinib, or asciminib
Y253H	Dasatinib, bosutinib, ponatinib, or asciminib
E255 V/K	Dasatinib, bosutinib, ponatinib, or asciminib
F359 V/I/C	Dasatinib, bosutinib, ponatinib, or asciminib
T315I	Ponatinib or asciminib

- **Primary resistance (no hematologic or cytogenetic response from the beginning of therapy)**
- **Secondary resistance (initial response that decays during the treatment).**

T315I mut and Ponatinib

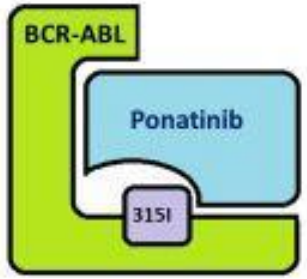
[Traditional Treatment (TKI) and Treatment Resistance due to Mutation]

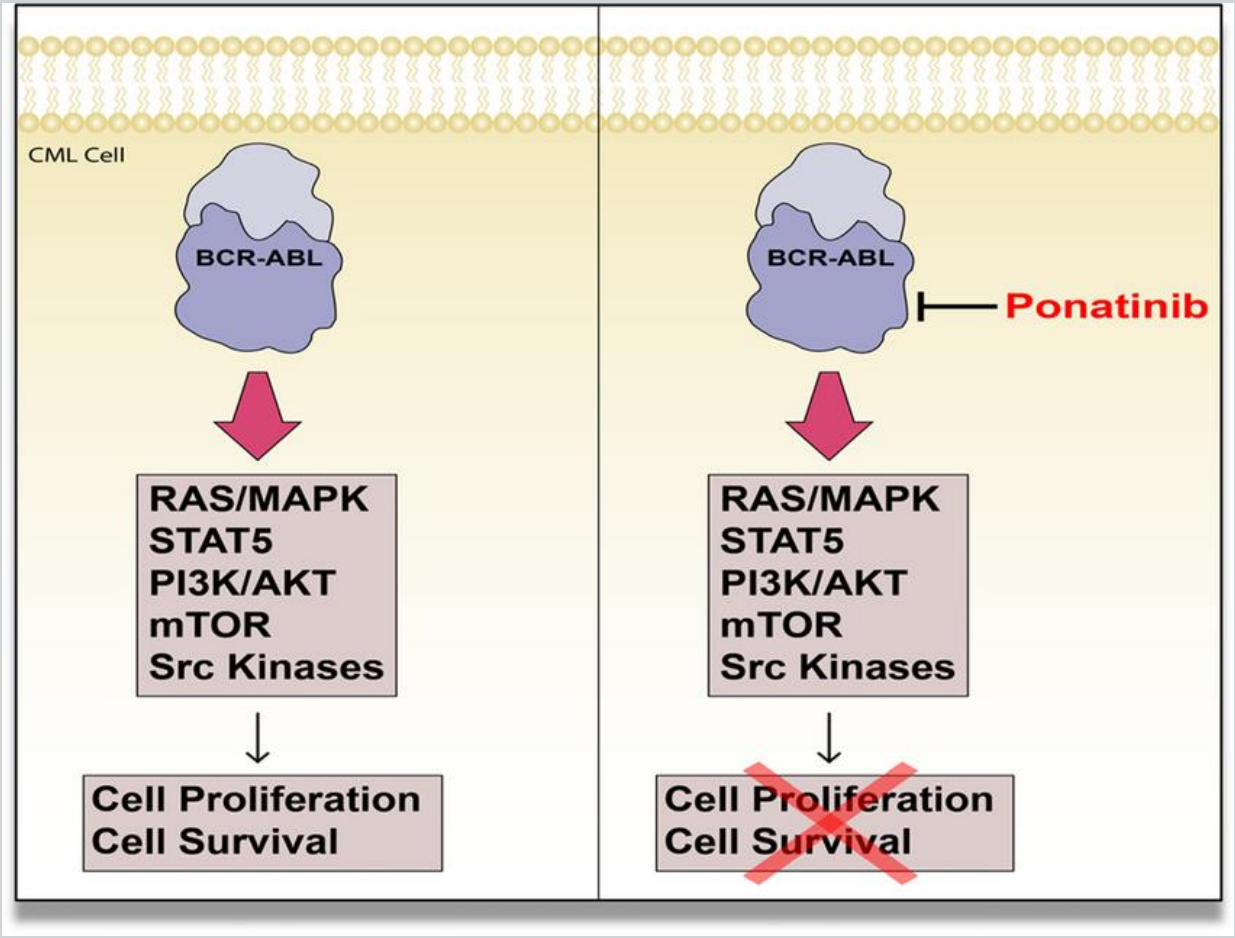


* T315I mutation: The 315th amino acid changes from threonine (T) to isoleucine (I)
If a T315I mutation occurs, traditional treatment (TKI) cannot bind to BCR-ABL and cannot elicit efficacy

[Efficacy of Ponatinib on T315I Mutations]

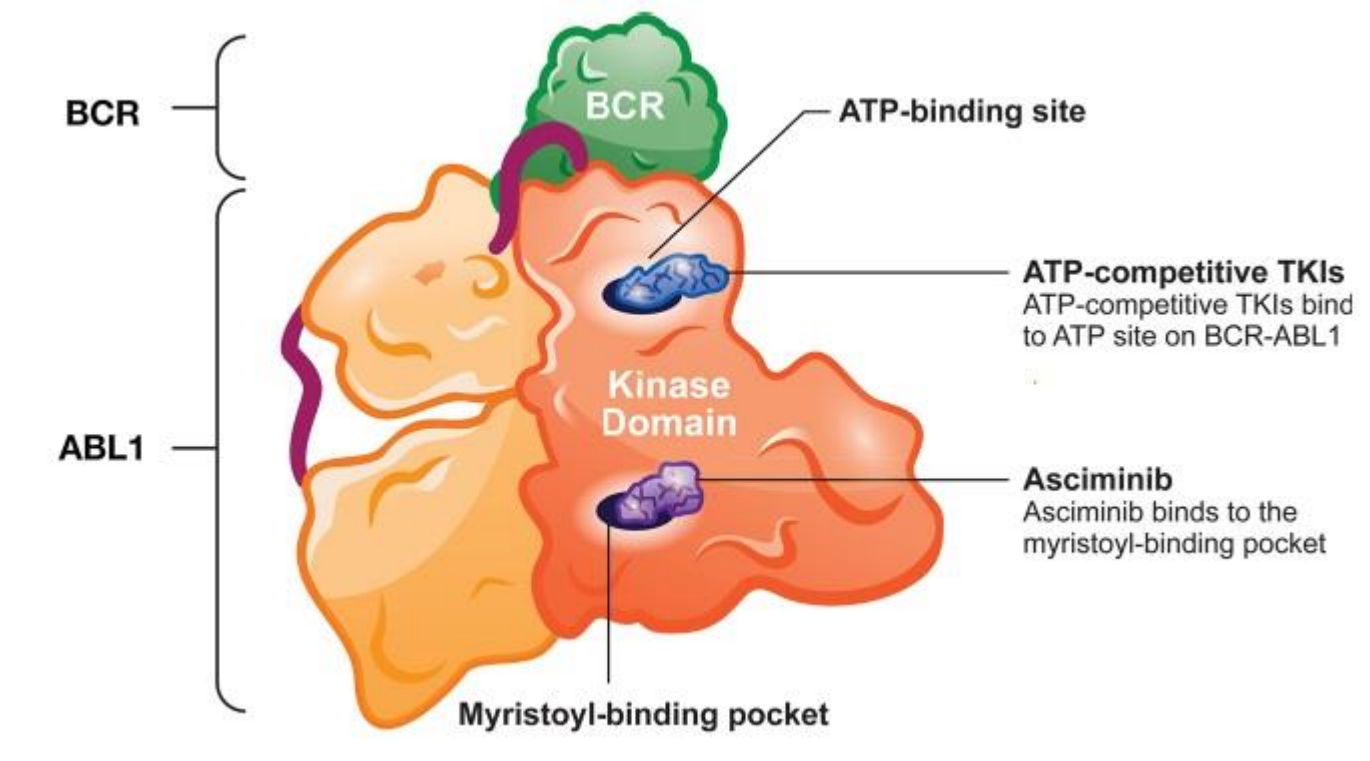
Ponatinib is effective in patients who have failed prior TKI therapy, at same time not influenced by the presence of T315I mutations and can bind with BCR-ABL and therefore elicit efficacy.





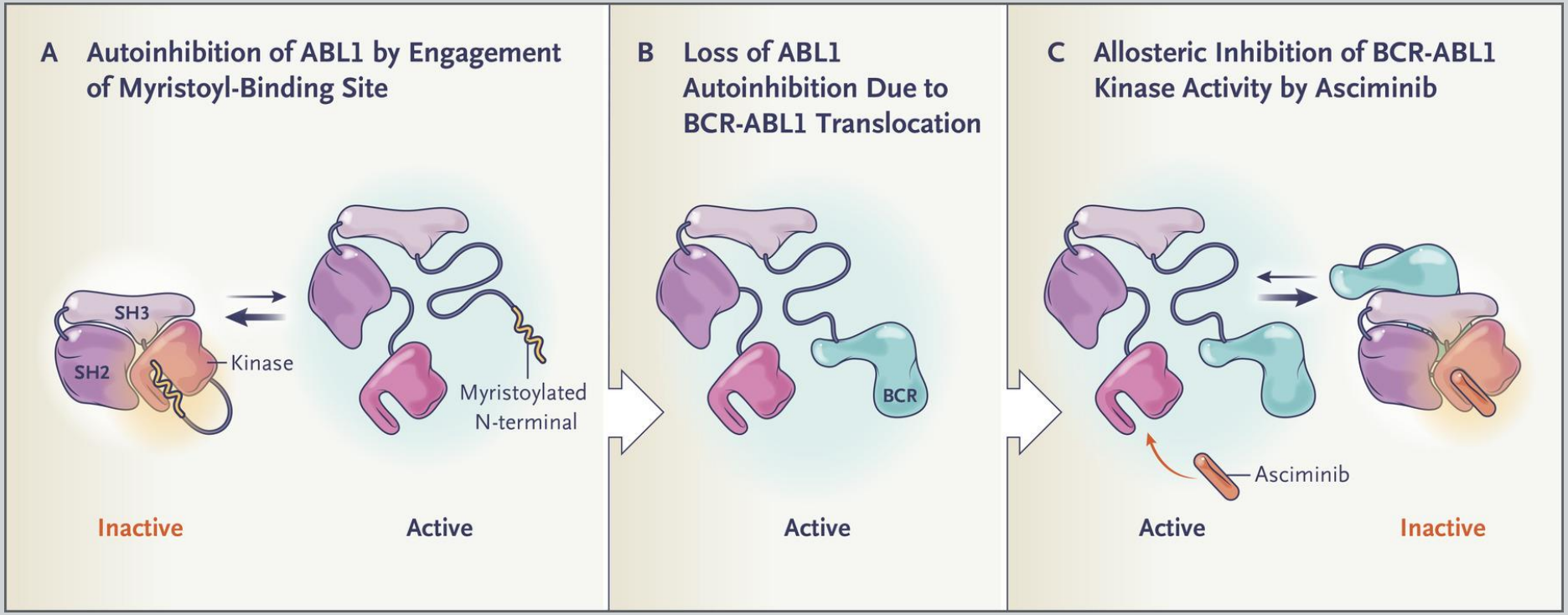
Ascimimib, a novel allosteric inhibitor of BCR-ABL1

First-in-class STAMP (Specifically Targeting the ABL Myristoyl Pocket) inhibitor



- **Asciminib's unique mechanism of action is distinct from ATP-competitive TKIs.**
- **Allosteric inhibitor of kinase activity: binding of the myristoyl site of the kinase domain (STAMP).**

Ascimimib: mechanisms of actions

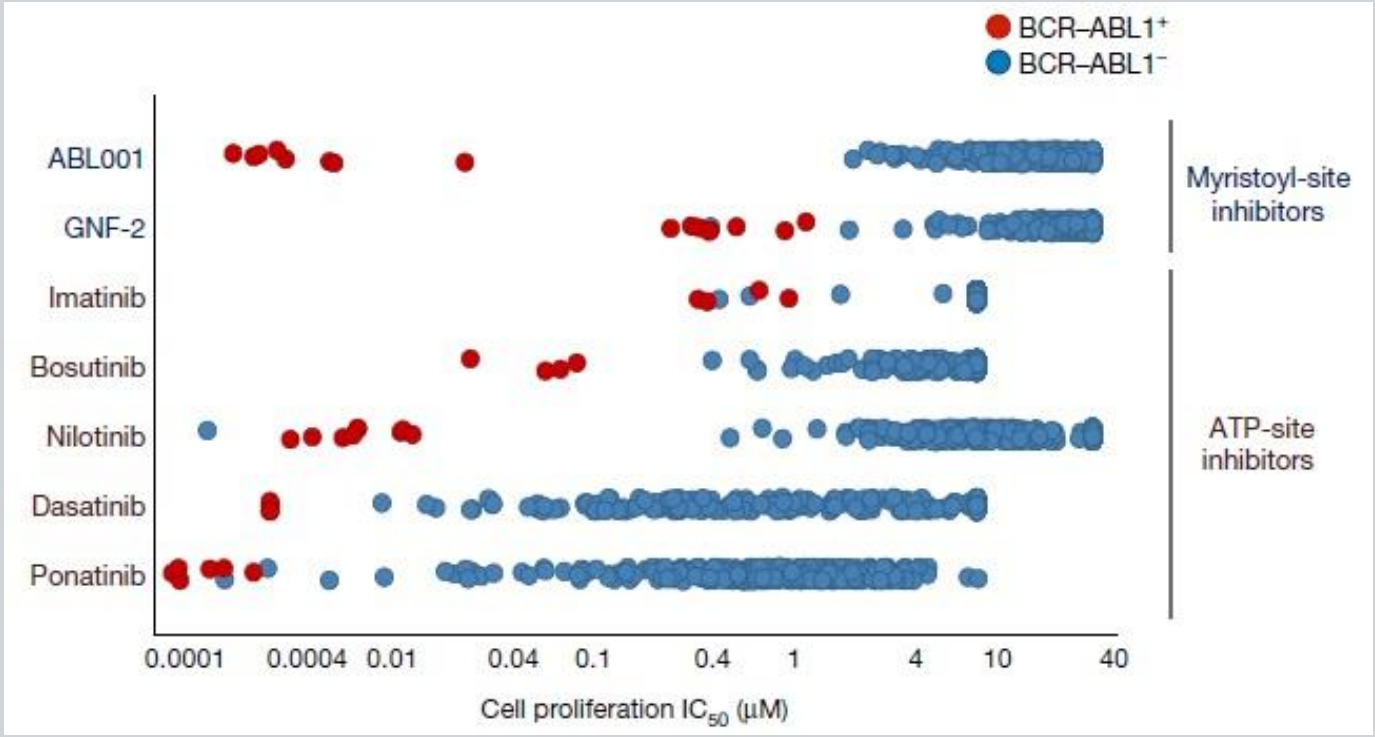


- **Locks BCR::ABL into an inactive conformation, inhibiting downstream signaling events.**
- **Target both native and mutated BCR::ABL1, including T315I mutant.**

Huges et al., 2019 N. Engl. J. Med.

Ascimimib: pre-clinical data

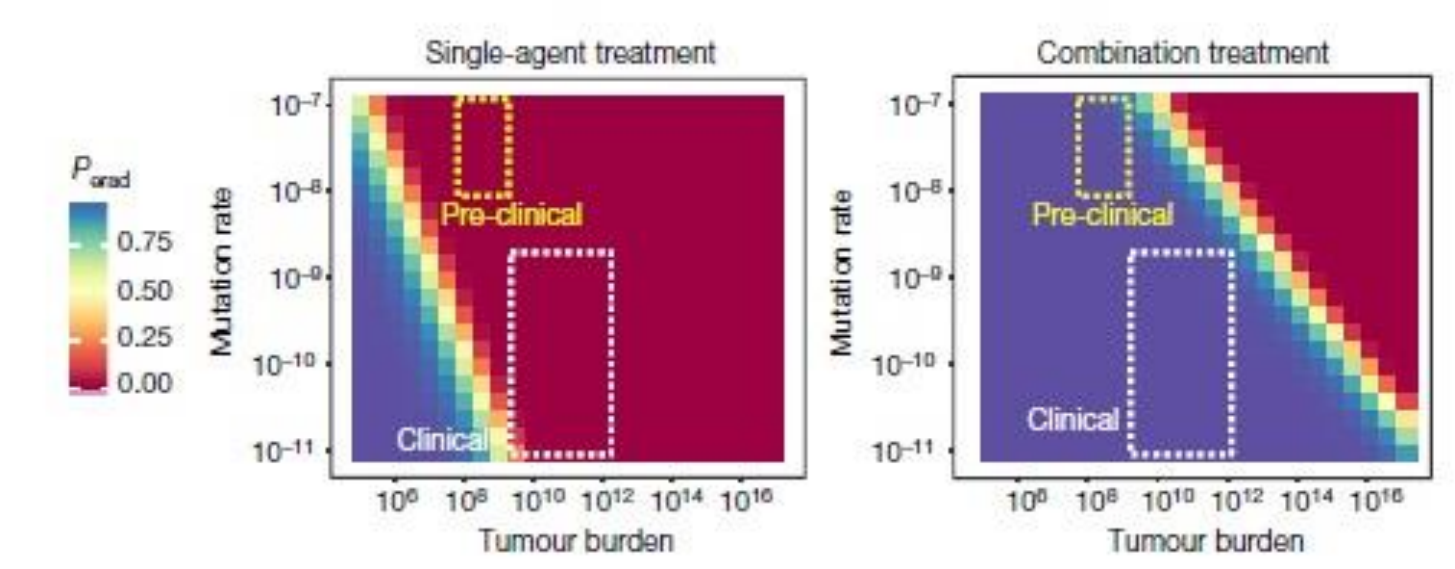
Ascimimib →



Asciminib was shown to have an improved selectivity profile vs 2 G TKIs, with a similar potency

Wylie, A.A., Nature 2017

Ascimimib: pre-clinical data

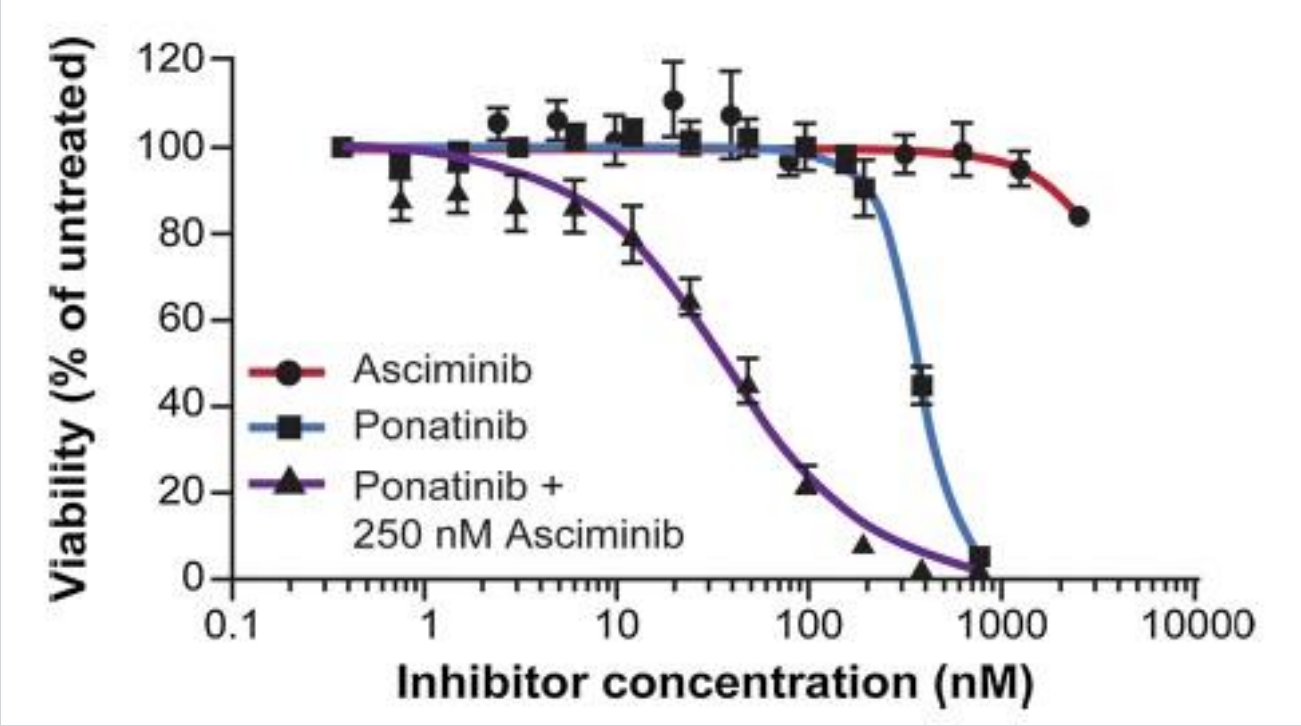


Ascimimib + Nilotinib

The non-overlapping resistance profiles of ascimimib and nilotinib enable durable tumour eradication when used in combination.

Wylie, A.A. et al, Nature 2017

Ascimimib: pre-clinical data

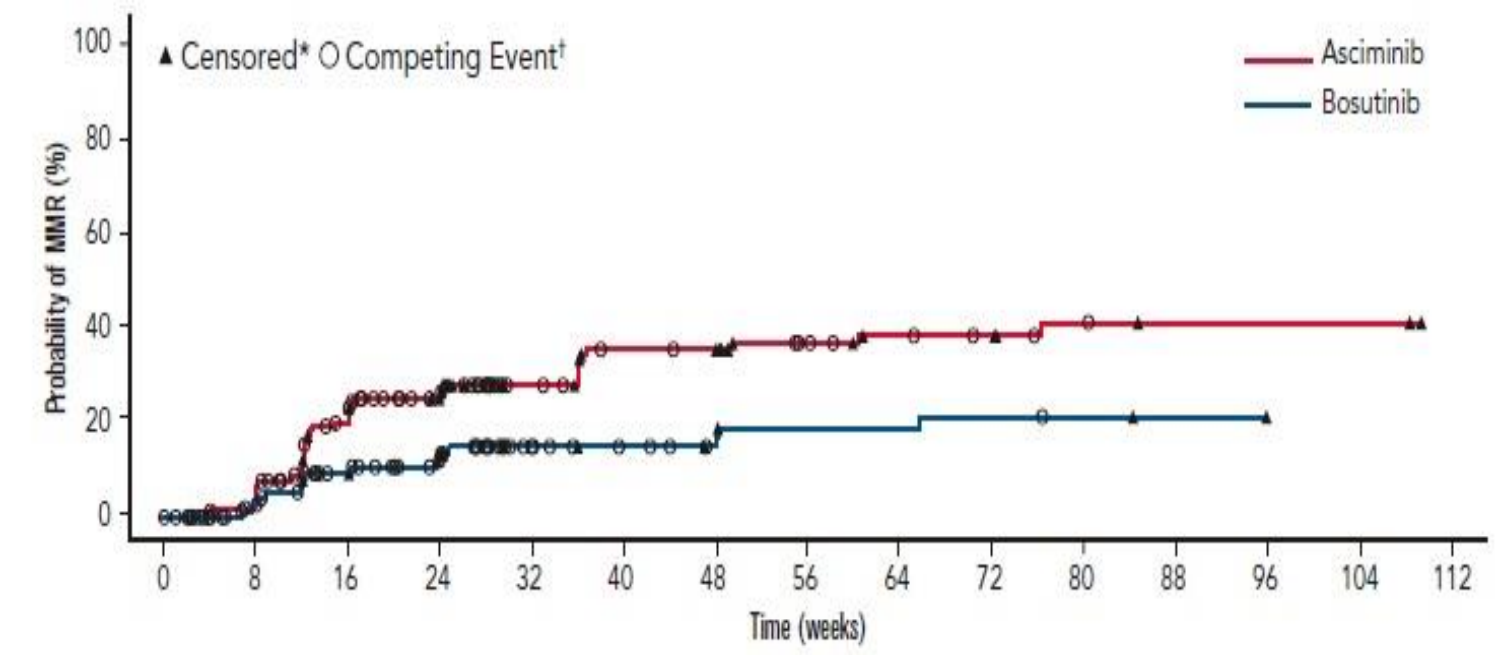


Ascimimib + Ponatinib

The cell proliferation curve for combination therapy shows markedly improved efficacy over monotherapy with either inhibitor.

Eide CA, et al. Cancer Cell. 2019

Ascimimib: clinical data

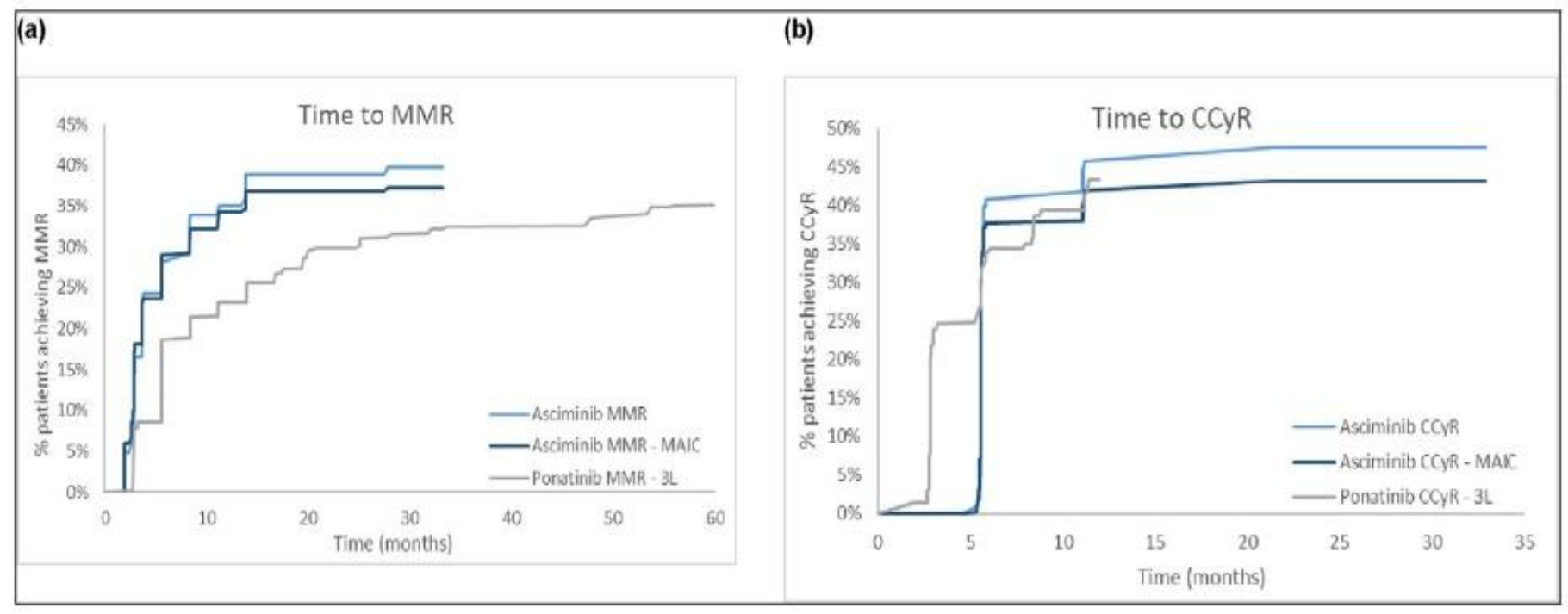


The cumulative incidence curve shows a statistically increase probability of achieving MMR for Ascimimib respect to Bosutinib

A third-line treatment option for CML in chronic phase with or without T315I mutation

Rea et al., Blood 2021

Ascimimib: clinical data



Ascimimib vs Ponatinib:
MMR 35%; 23%
CCyR 46%; 43%

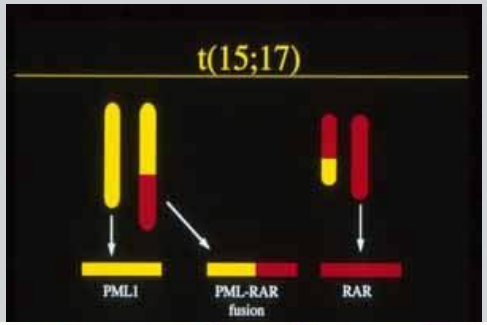
Increase probability of achieving MMR for Ascimimib respect to Ponatinib

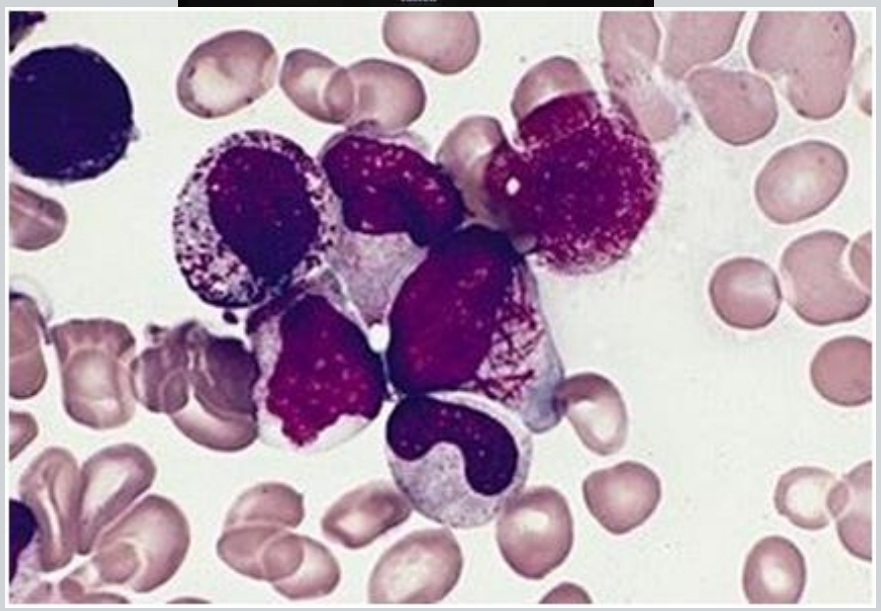
Atallah E et al., J Cancer Res Clin Oncol. 2023

PML-RARalpha as target of ATRA therapy

Acute promyelocytic leukemia

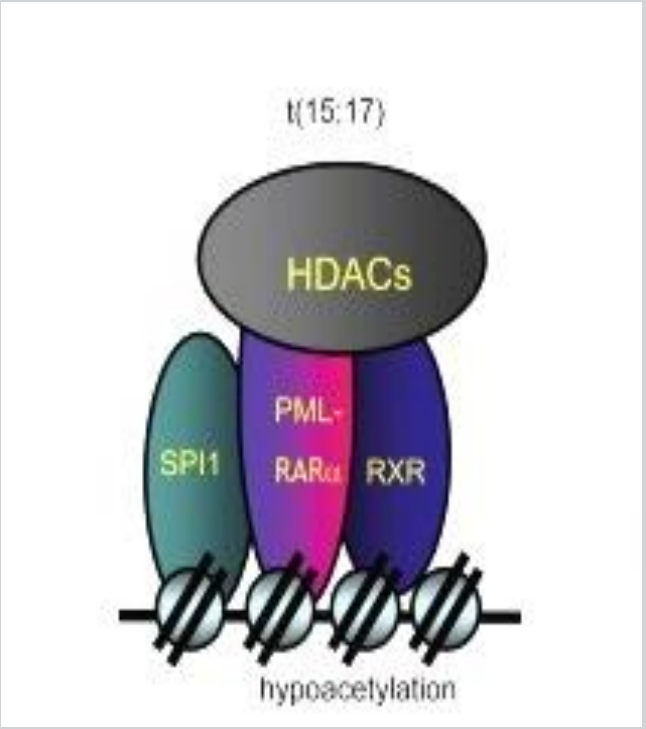
Acute promyelocytic leukemia (APL)





- Hematological emergency with severe hemorrhagic syndrome. Average onset at 40 years.
- APL is a variant of Acute Myeloid Leukemia, specifically subtype M3 (15% of AML cases)
- Characterized by t(15;17): PML-RARα fusion
- Patients with APL suffer from an accumulation of immature granulocytes or promyelocites in their blood and bone marrow

t(15;17)(q22;q12)



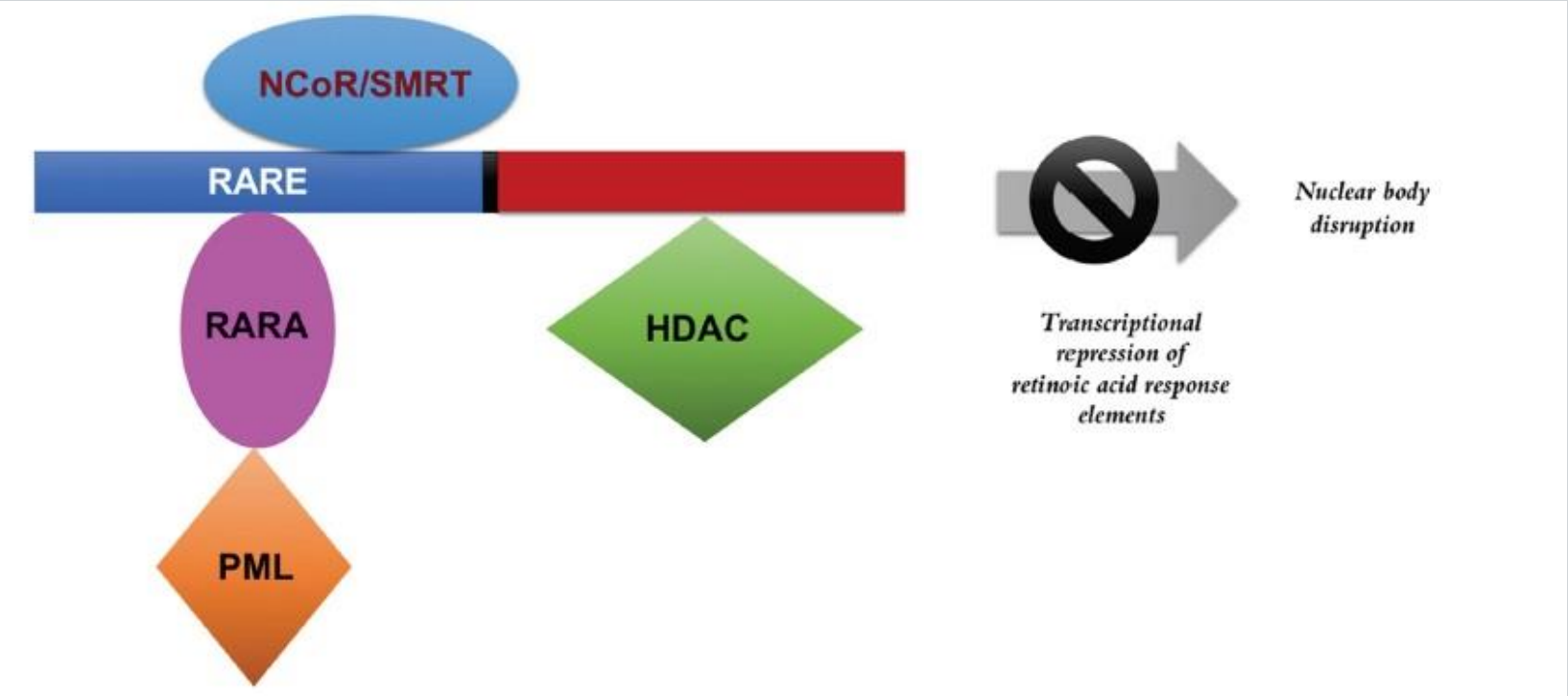
PML-RARalfa

PML: promyelocytic leukemia gene. Ruolo nell'ematopoiesi precoce.

RARalfa: retinoic acid receptor-alpha. Agisce sia come attivatore che come repressore trascrizionale.

PROGNOSI: positiva

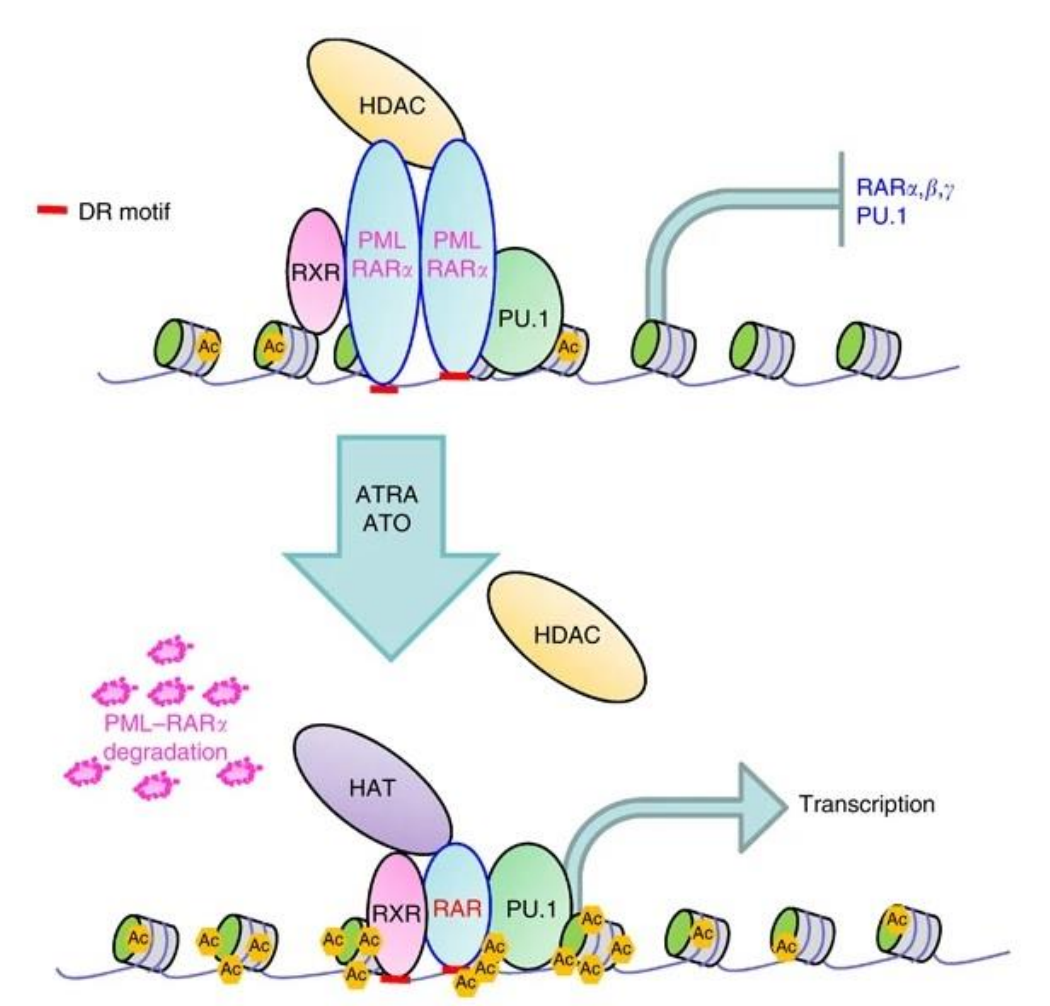
t(15;17)(q22;q12)



PML-RARalfa è un repressore trascrizionale costitutivamente attivo che regola l'espressione di geni coinvolti nella differenziazione, apoptosi e nel self-renewal.

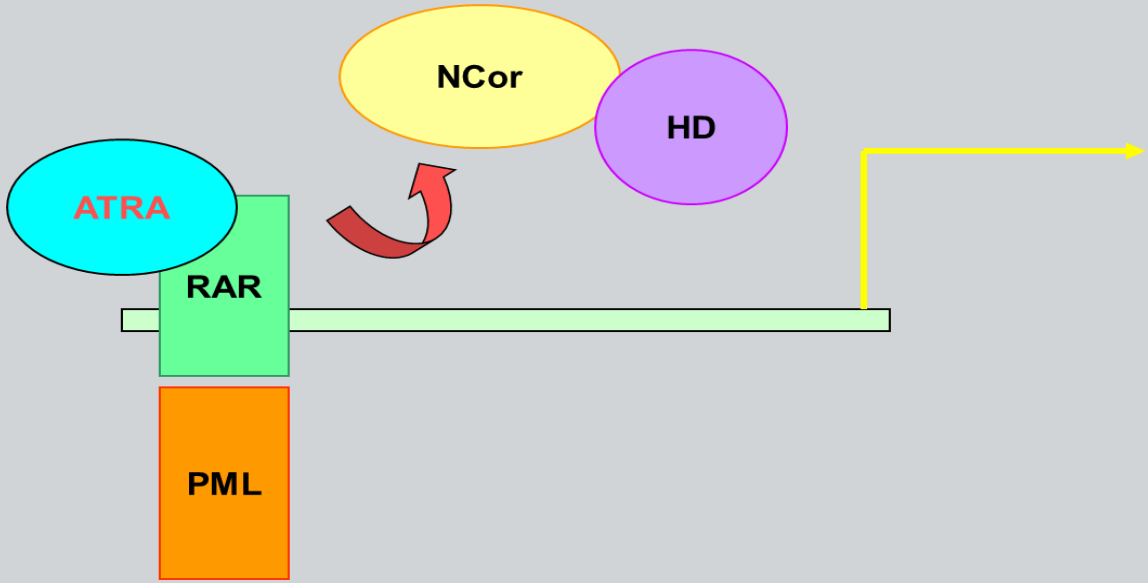
Ipoacetilazione costante dei geni target

APL therapy

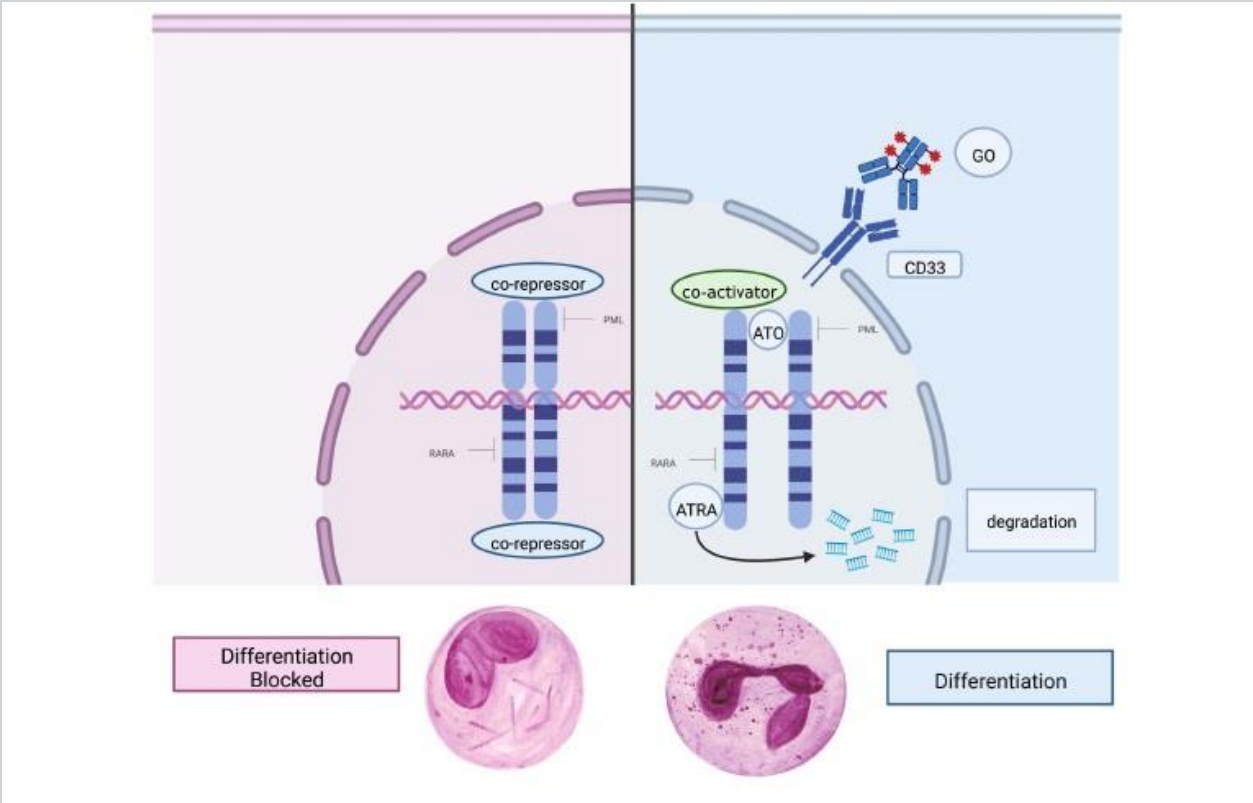


ATRA lead to a sustained expression of target genes leading to terminal differentiation of promyelocytes

CHEMO-FREE TREATMENTS



APL therapy



ATRA + ATO

ANTI-CD33 (high risk): immune therapy

Only chemotherapy

POOR PROGNOSIS

TARGET THERAPY

GOOD PROGNOSIS

Mutated JAK2 as target of Ruxolitinib

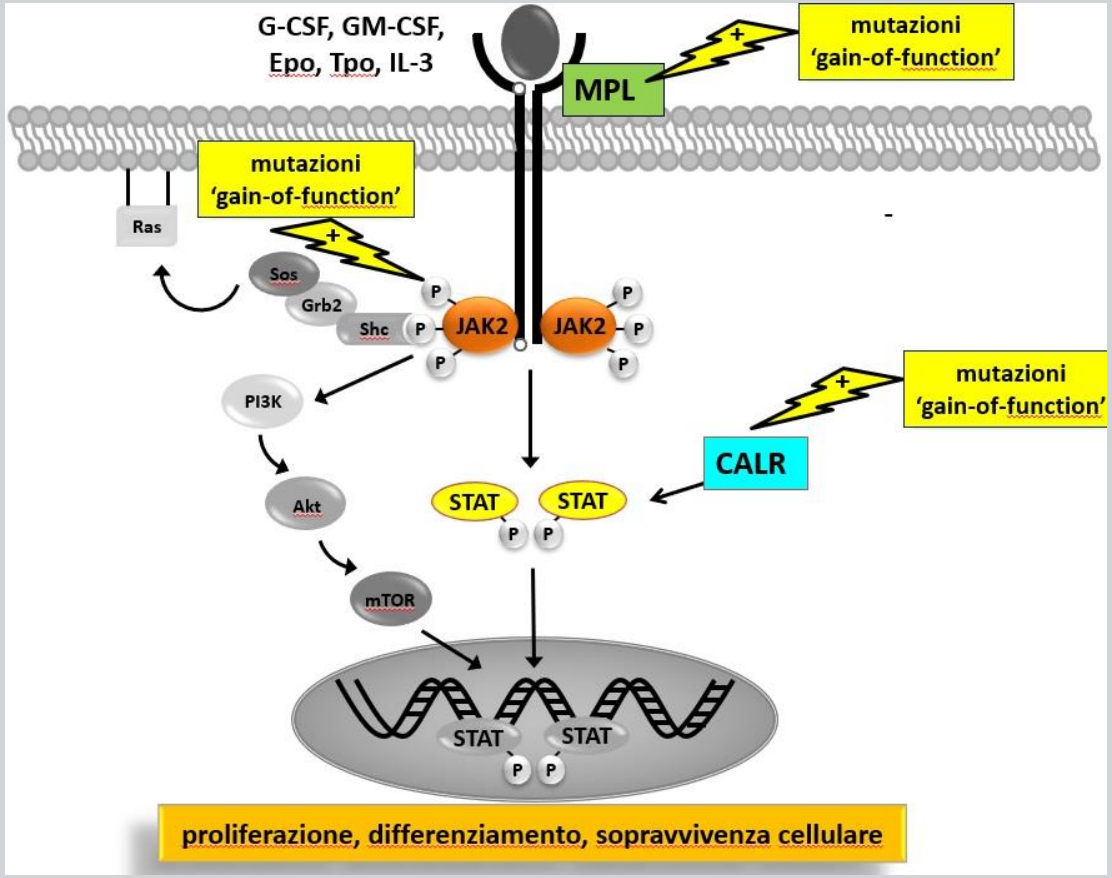
Myeloproliferative Neoplasms

Myeloproliferative Neoplasms (MPNs)

JAK2

CALR

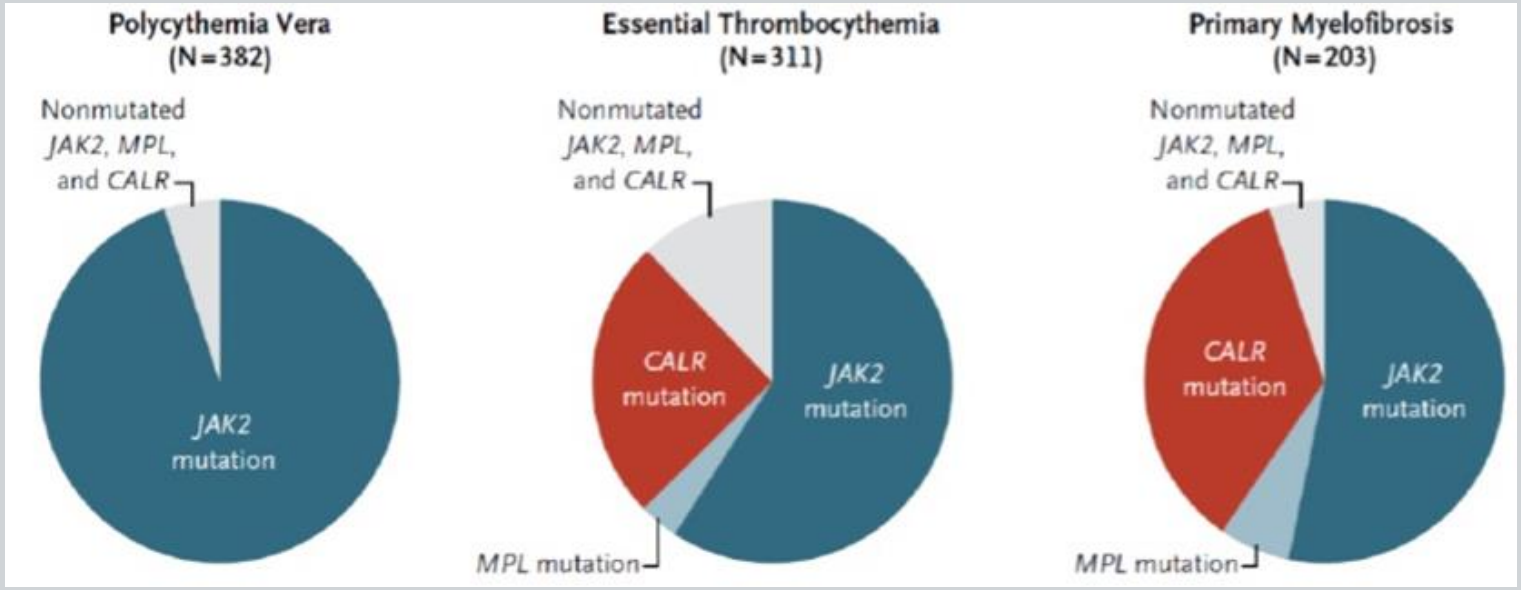
MPL



- Uncontrolled myeloproliferation
- Abnormally elevated levels of circulating proinflammatory cytokines

JAK-STAT SIGNALLING PATHWAY CONSITUTELY ACTIVATED

Myeloproliferative Neoplasms (MPNs)



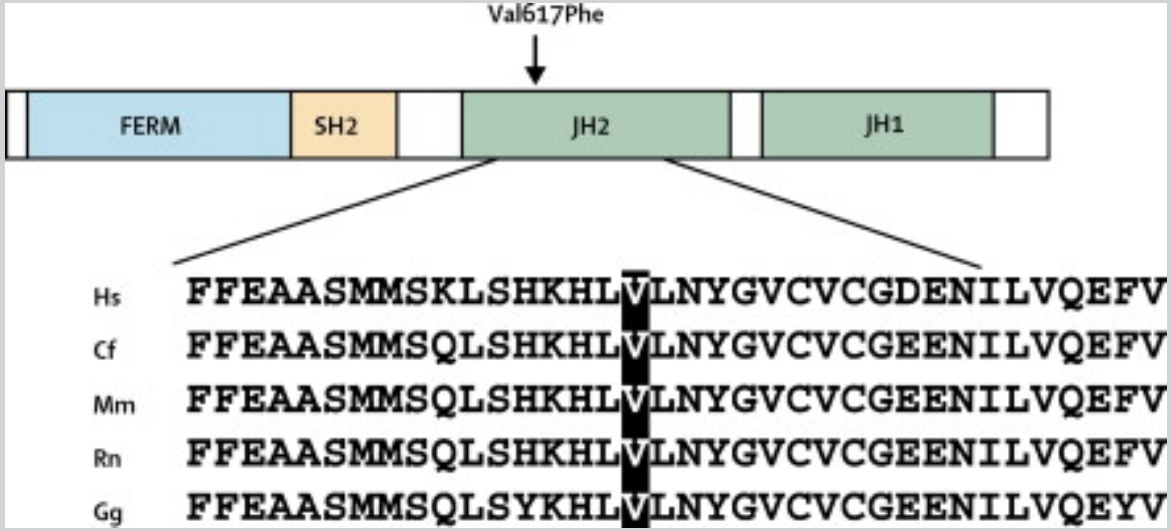
Possibilità di tripli negativi

Mutazioni di **JAK2**, **MPL** e **CALR** forniscono oggi un marcatore genetico utile per la diagnosi del 99 % di PV e dell'85% delle TE e MF

JAK2 in MPNs

- Tirosino-chinasi che trasduce il segnale dei fattori di crescita emopoietici (eritropoietina e trombopoietina).
- Mutazioni attivanti che inducono attività recettoriale costitutiva (indipendente da TPO e EPO).

JAK2 V617F
(esone 14 cromosoma 9)

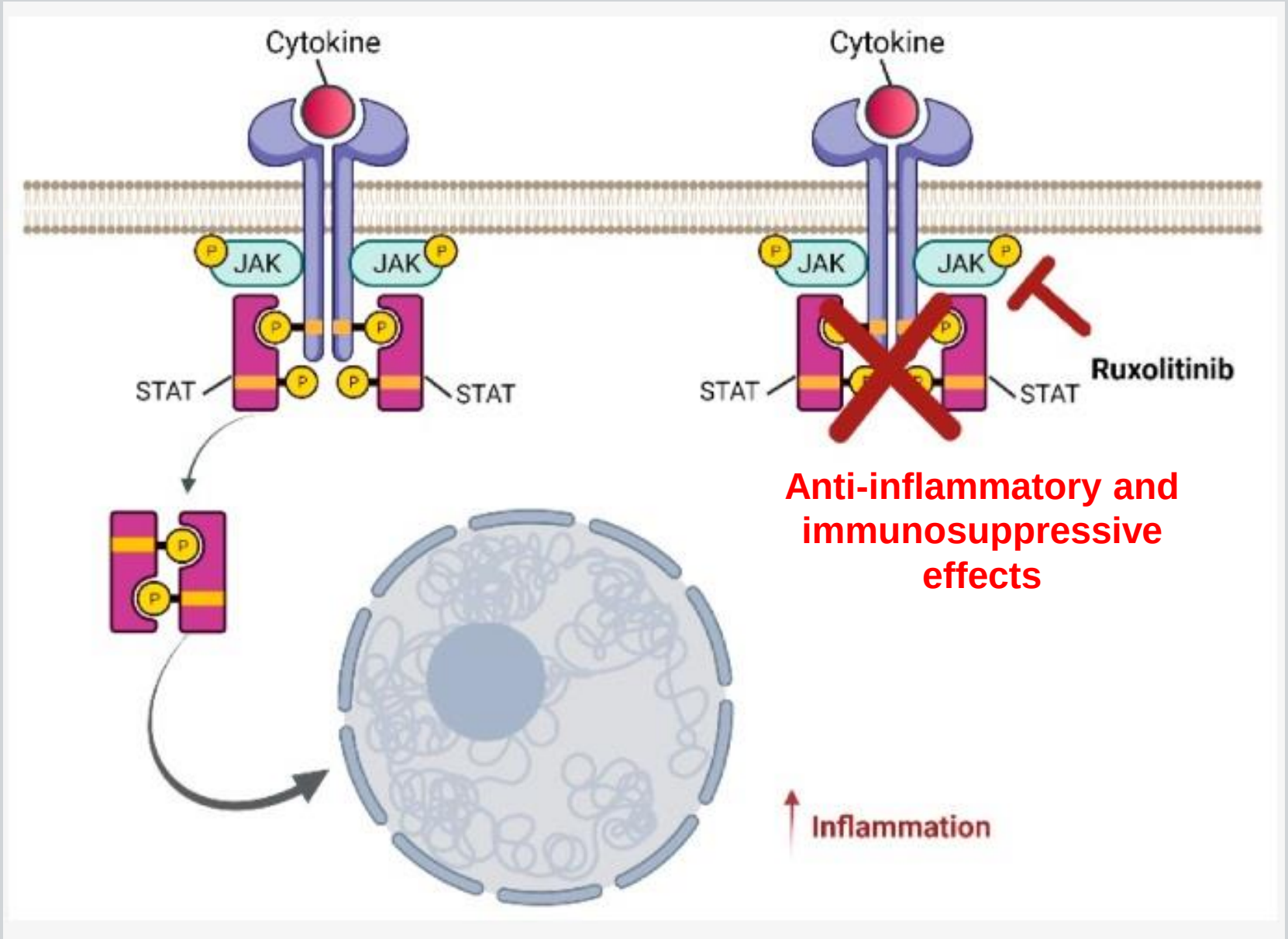


Incidenza diversa nelle patologie:
95% PV, 60 % TE e MF

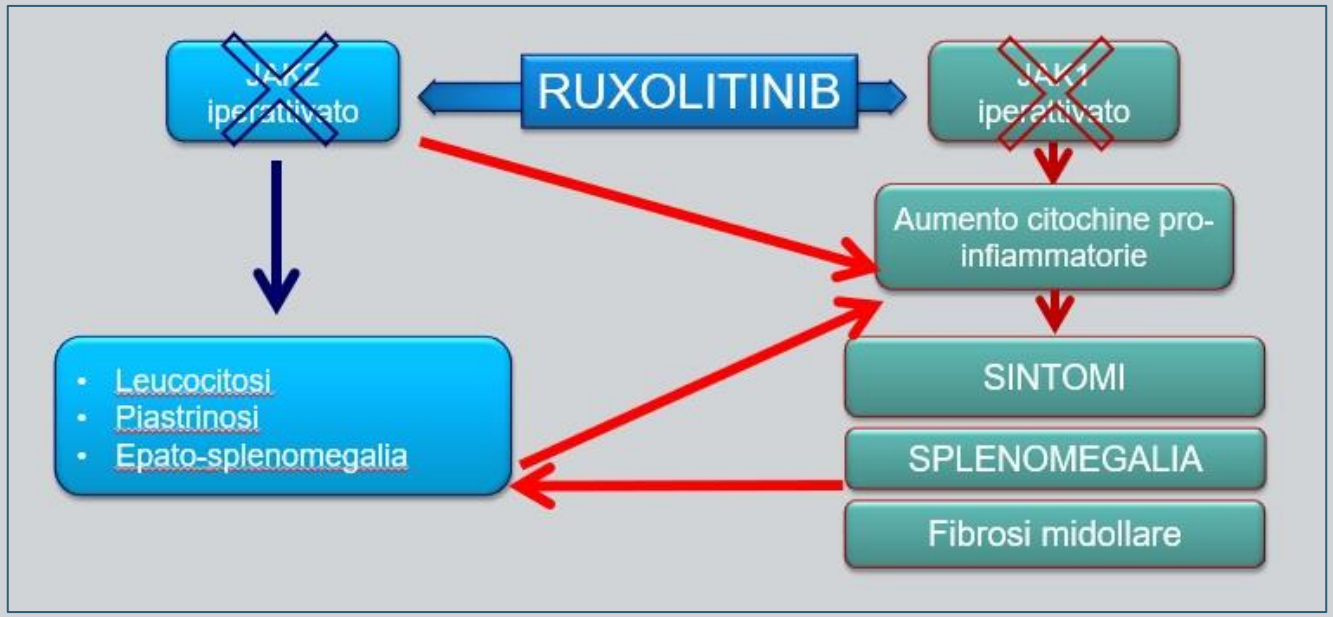
Baxter et al Lancet 2015

Ruxolitinib: inhibitor of JAK2 and JAK1 protein kinases

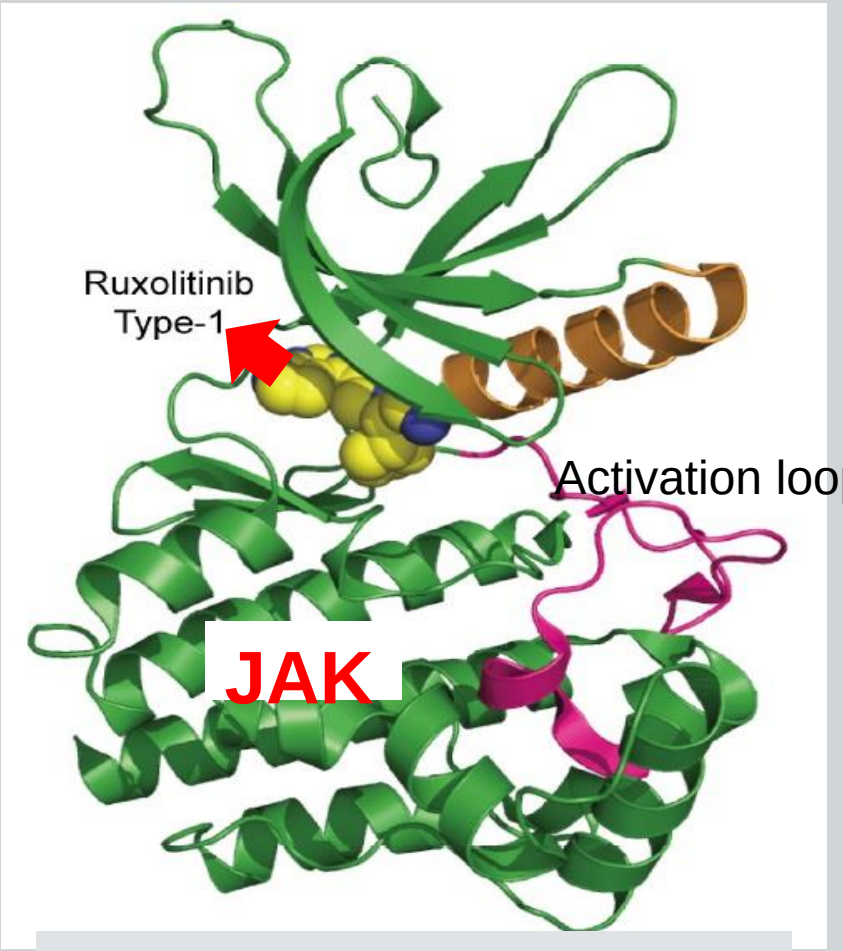
- Intermediate- or high risk MF
- Post-PV; PV not responding to hydroxyurea
- Post-essential thrombocythemia MF



Ruxolitinib: inhibitor of JAK2 and JAK1 protein kinases



- JAK2 is essential for regulating cell proliferation, particularly of hematopoietic cells (red blood cells, white blood cells, megakaryocytes and platelets).
- JAK1 is the main mediator of the production of substances (cytokines) that are normally released during infections and inflammation.



Type I inhibitors target the ATP-binding site of the JAKs under the active conformation of the kinase domain

Ruxolitinib: mechanism of actions

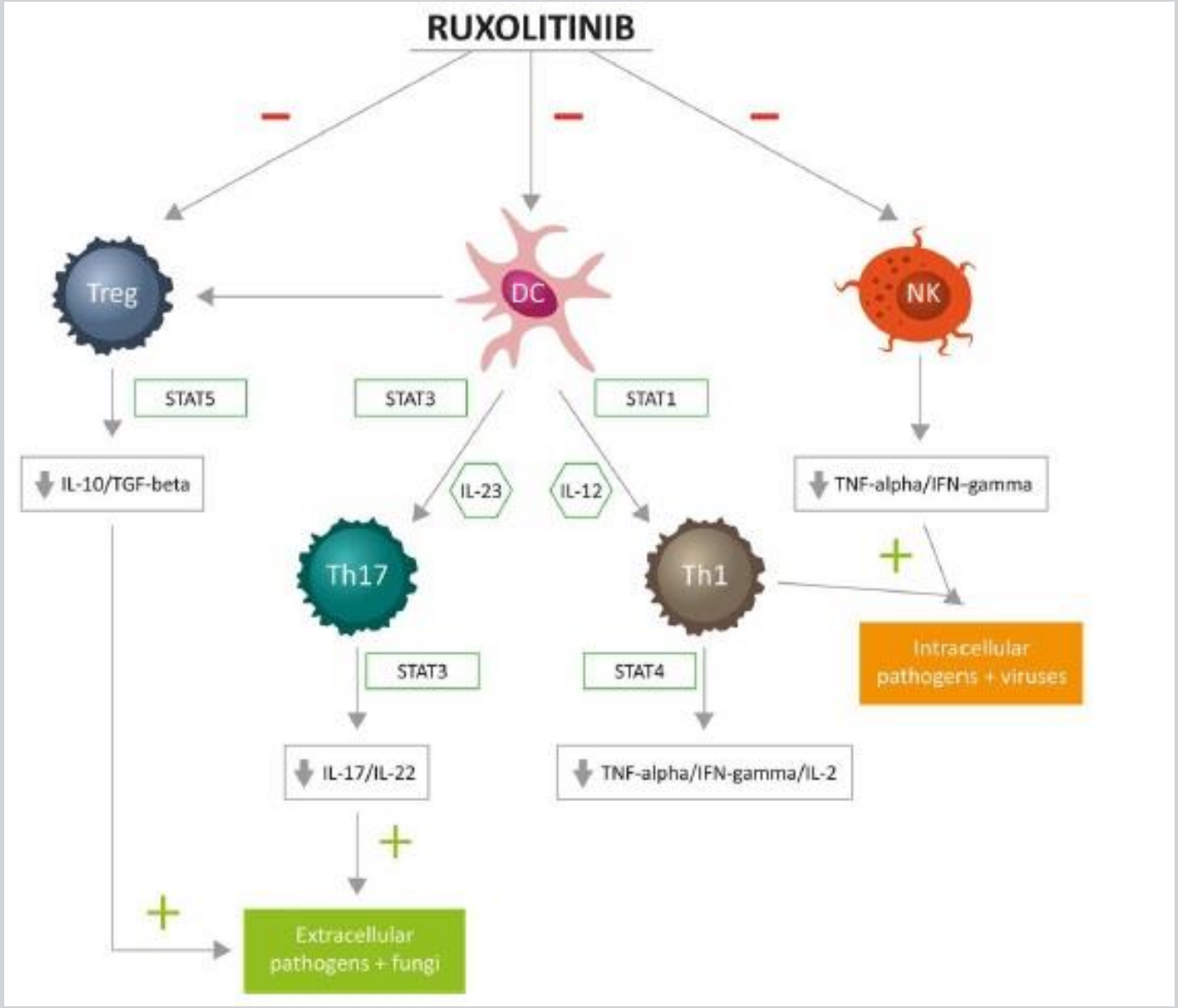
Reduction of proinflammatory cytokines

⇩

Improvement of symptoms, quality of life and, ultimately, bone marrow fibrosis

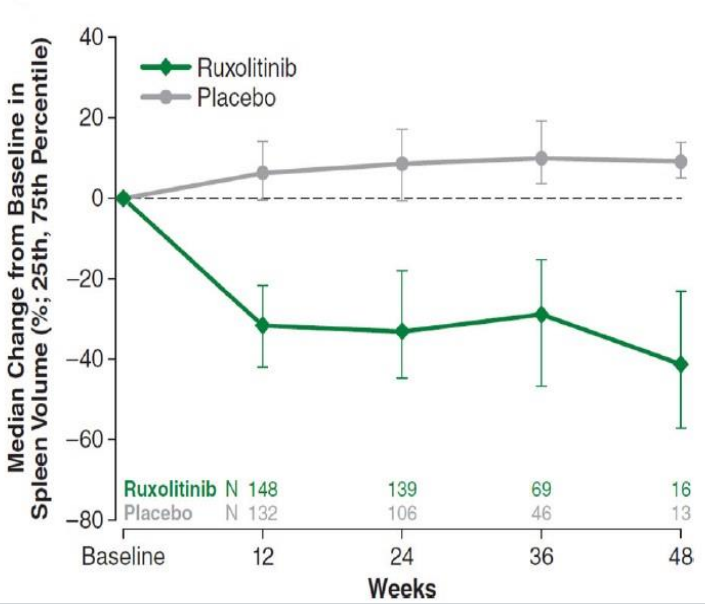
✗ **Infections complications and hematological and solid tumors**

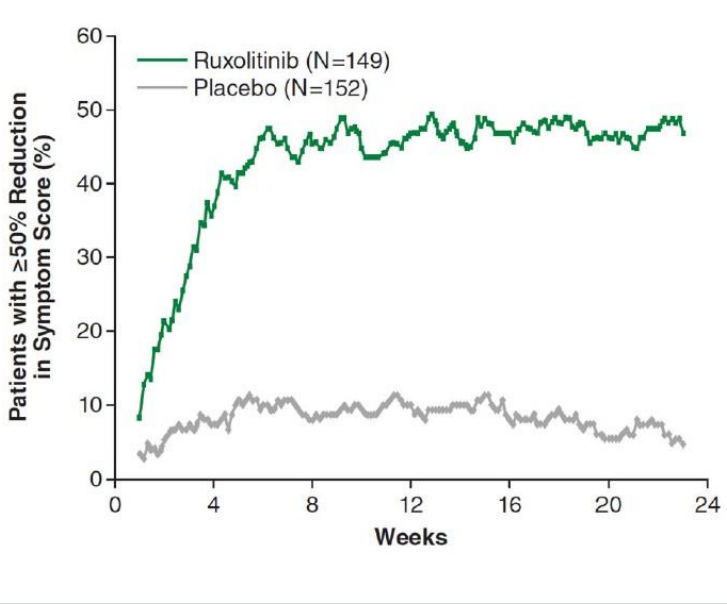
✓ **Use in GVHD**

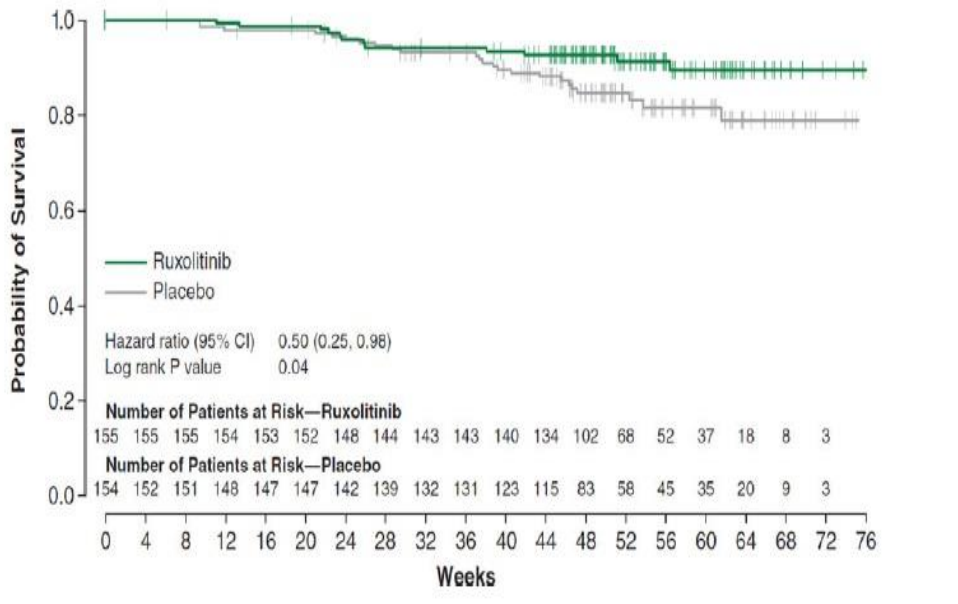


Ruxolitinib for MF

COMFORT I STUDY





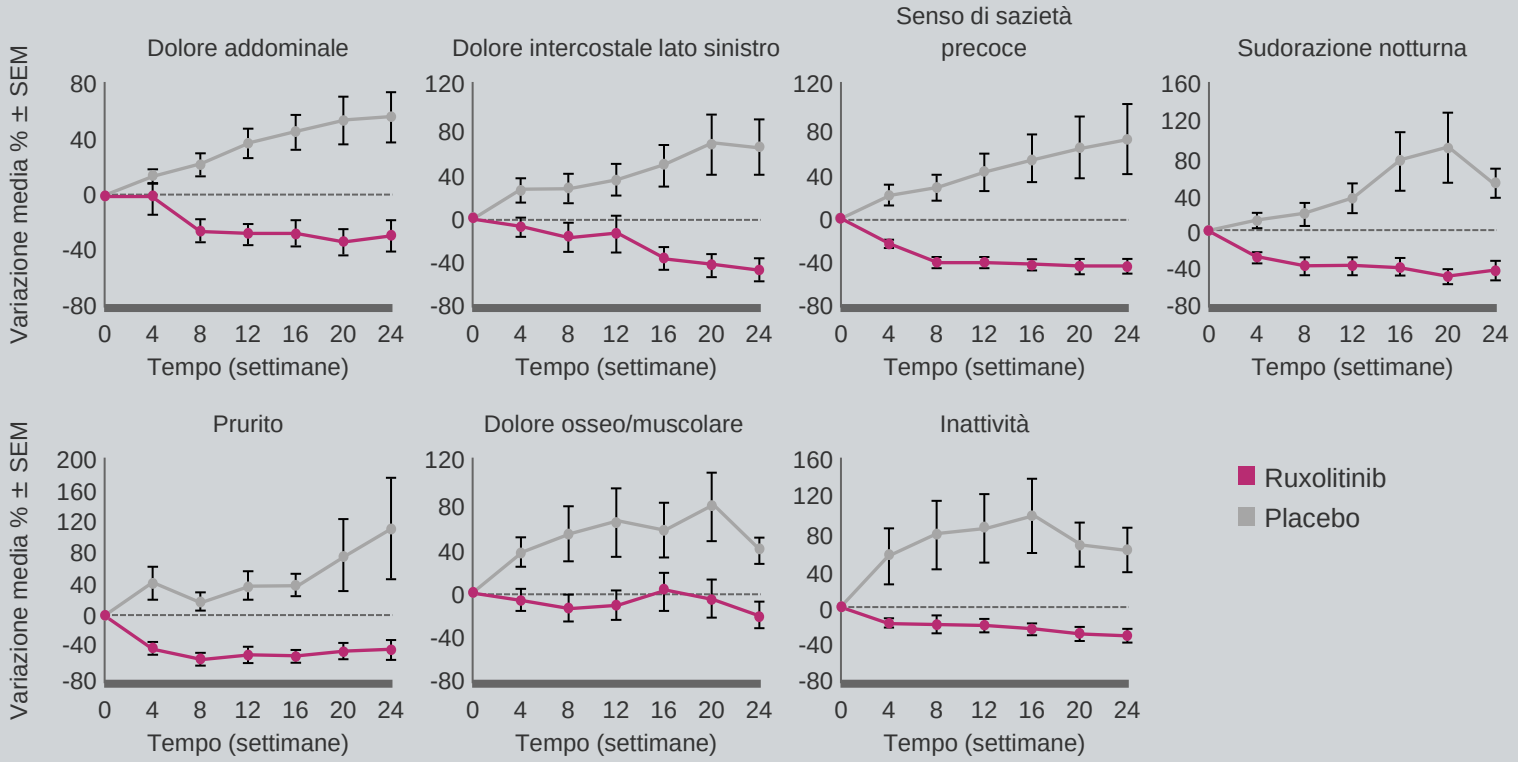


- ❑ **Control of myeloproliferation**
- ❑ **Reducing splenomegaly and symptoms**
- ❑ **Inhibition of both wild type and JAK2V617F mutation (suppression of STAT3)**
- ❑ **In some cases, reducing JAK2V617F allele burden**

Verstovsek et al. N Engl J Med 2016
Cervantes F. et al, Blood 2013

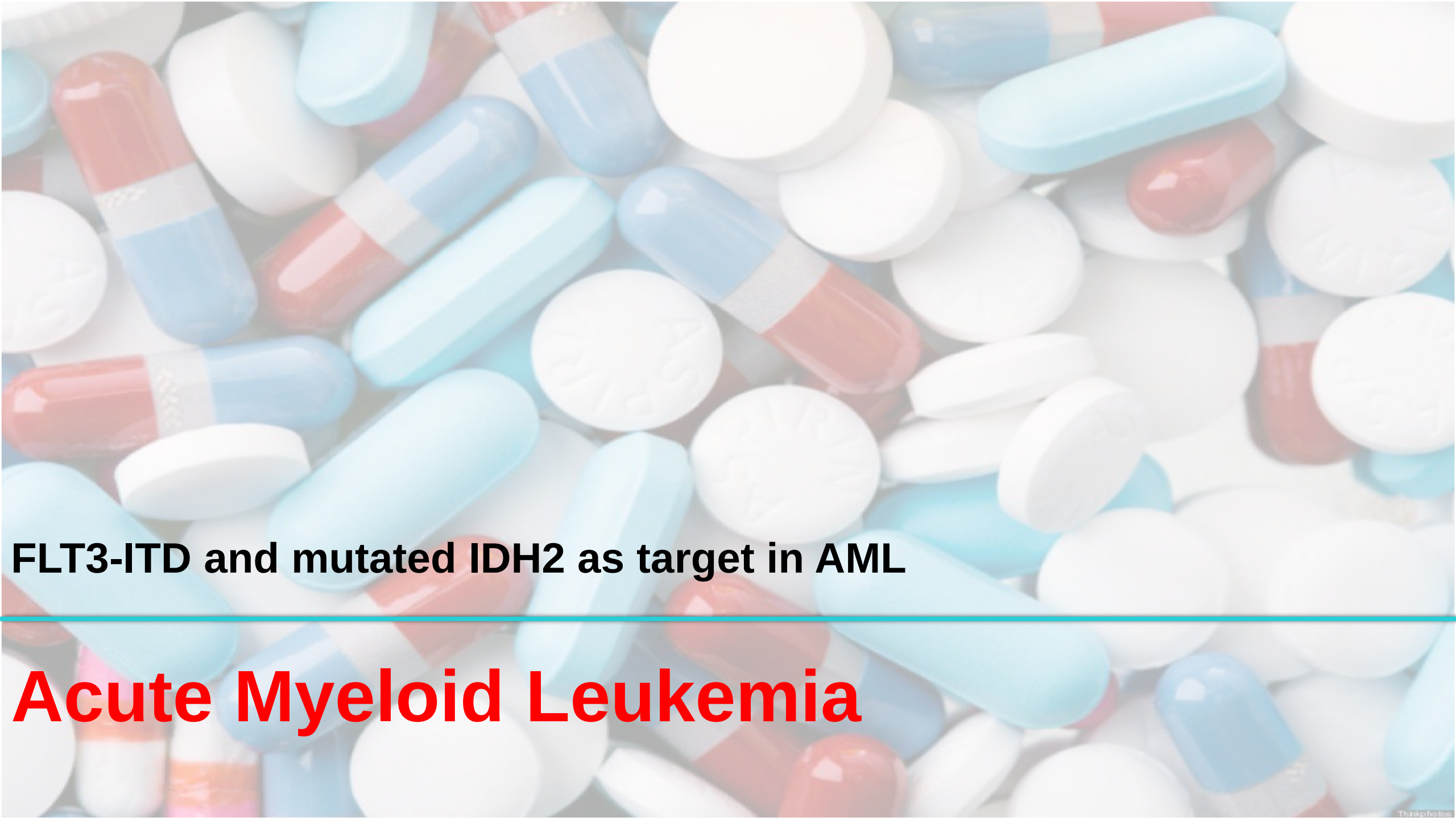
Ruxolitinib for MF

COMFORT I STUDY



- Patients treated with ruxolitinib report rapid improvement of all symptoms.
- 91.2% of patients with TSS ≥50% defined their status as “very improved” or “definitely much improved”

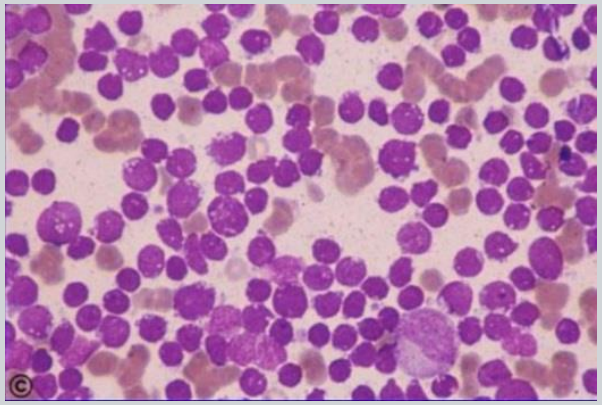
1.Mesa RA, et al. J Clin Oncol 2013; 31(10): 1285-92.

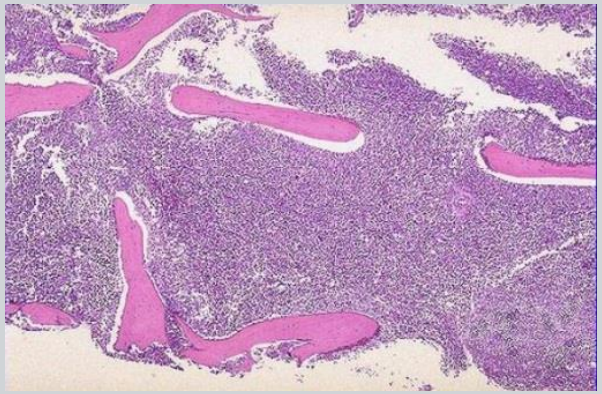


FLT3-ITD and mutated IDH2 as target in AML

Acute Myeloid Leukemia

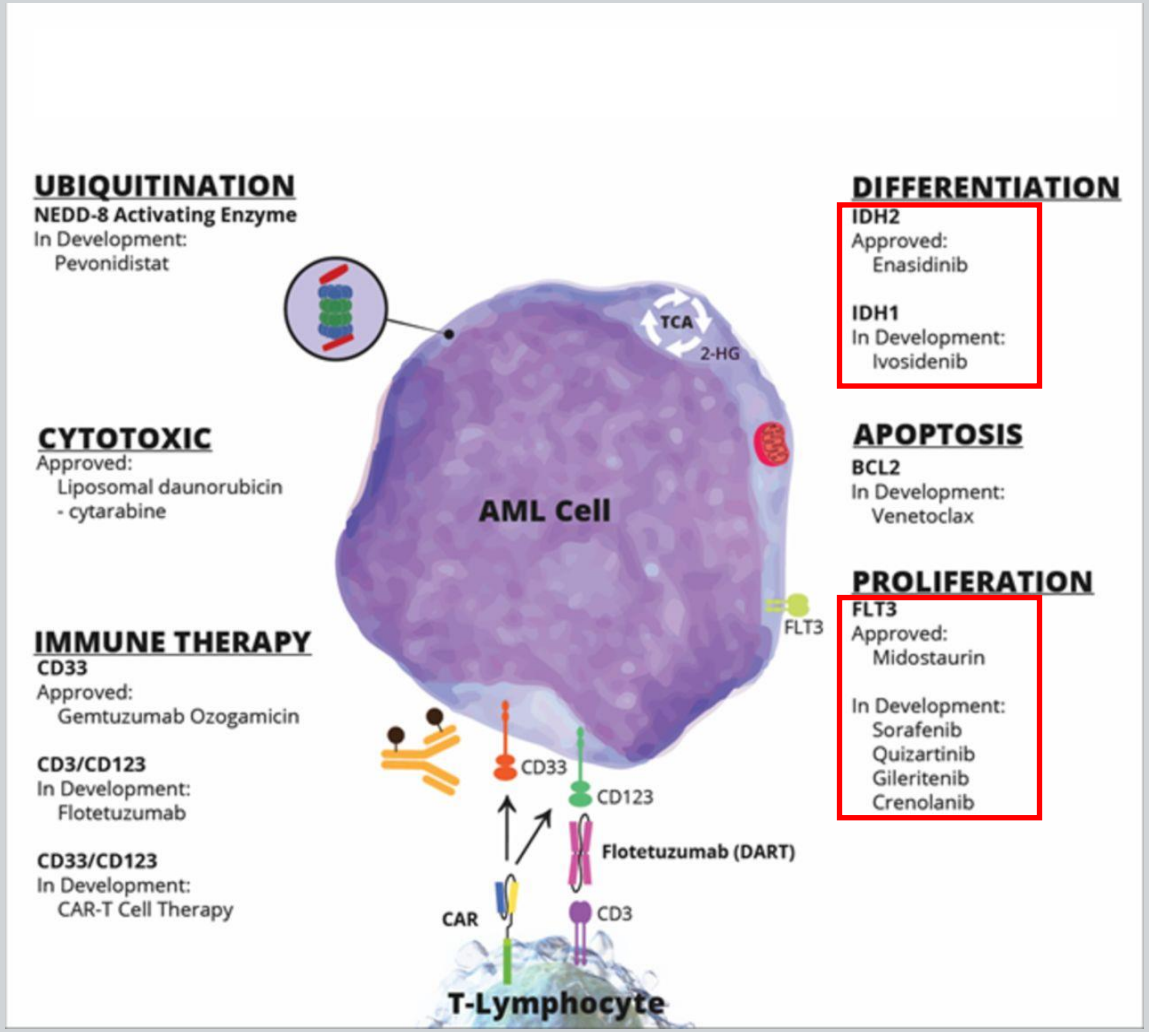
Acute Myeloid Leukemia (AML)

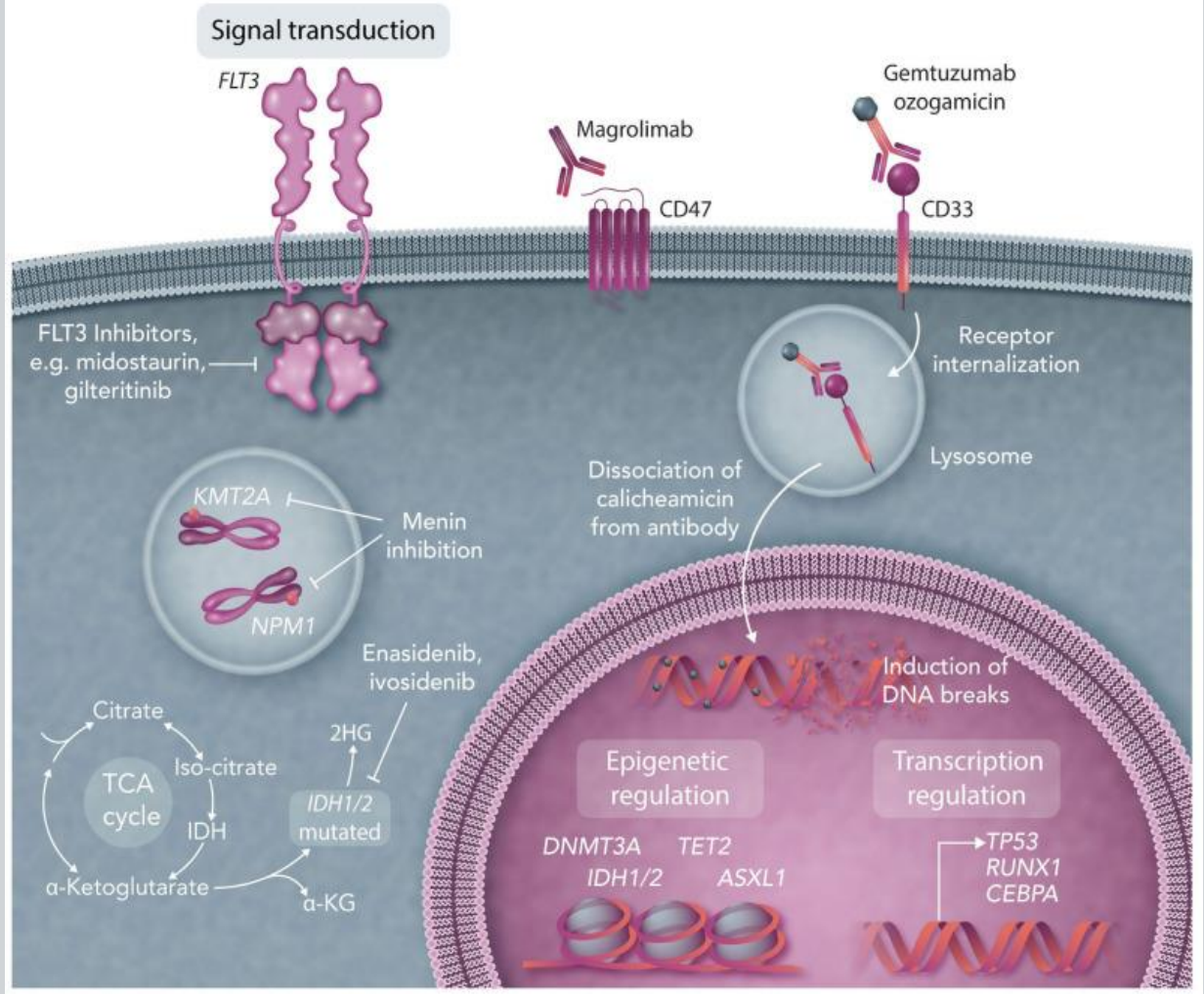




- Clonal expansion of undifferentiated myeloid precursors in the bone marrow and resultant failed hematopoiesis.
- Genetically heterogeneous malignancy comprised of various cytogenetic and molecular abnormalities that has notoriously been difficult to treat with an overall poor prognosis.
- Increased understanding of the genetic underpinnings of AML has led to targeting actionable mutations.

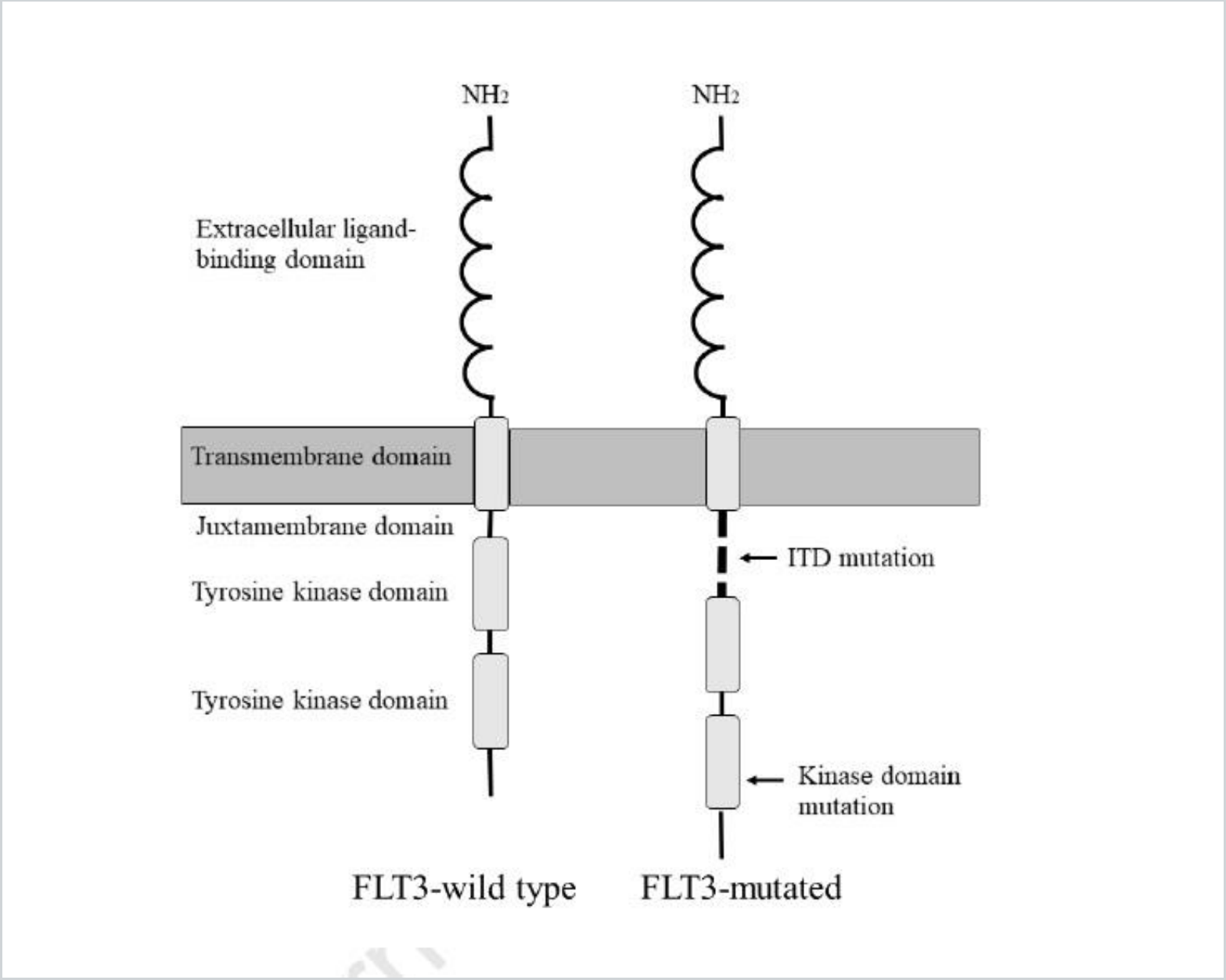
AML Target Therapy





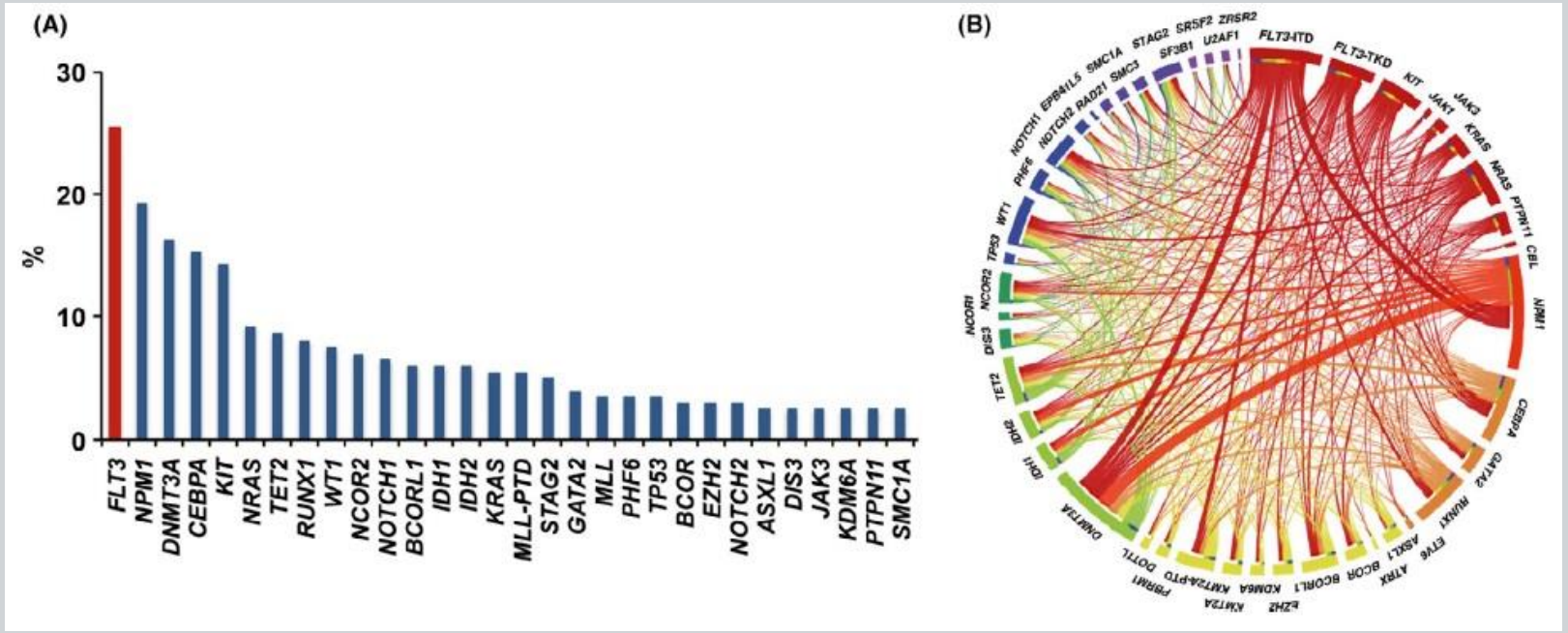
FLT3

- FMS-related tyrosine kinase 3 gene (FLT3) is one of the most highly recurrently mutated genes in AML and one of the earliest discovered.



FLT3

- FLT3 frequently co–occurs with NPM1, DNMT3A, IDH1/2, TET2, GATA2 and KMT2A-partial tandem duplication mutations.
- Mutually exclusive with KIT, K/NRAS and CEBPA-double (CEBPA-D) mutations.

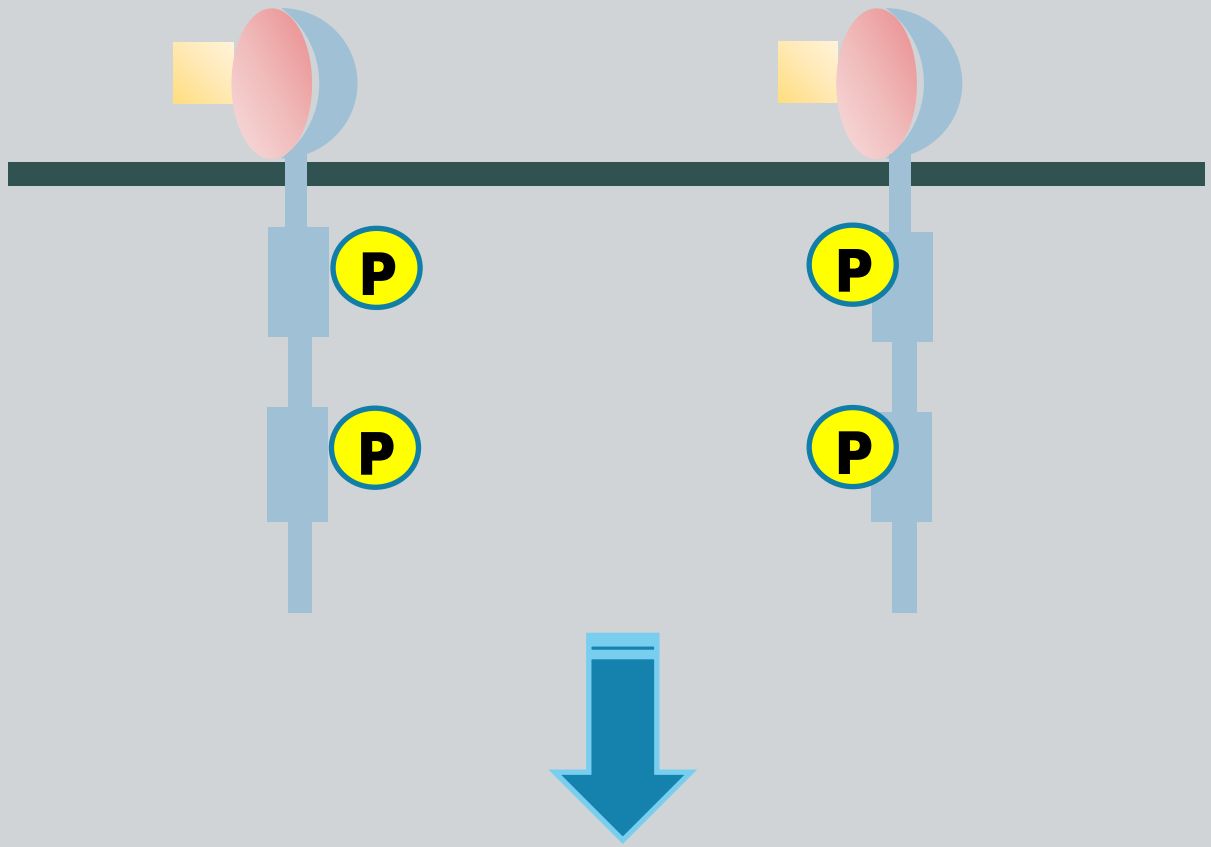


Genetic alterations in AML identified by NGS

Mutations that confer a proliferative and/or survival advantage to hematopoietic progenitors
+
Mutations that impair hematopoietic differentiation

FLT3

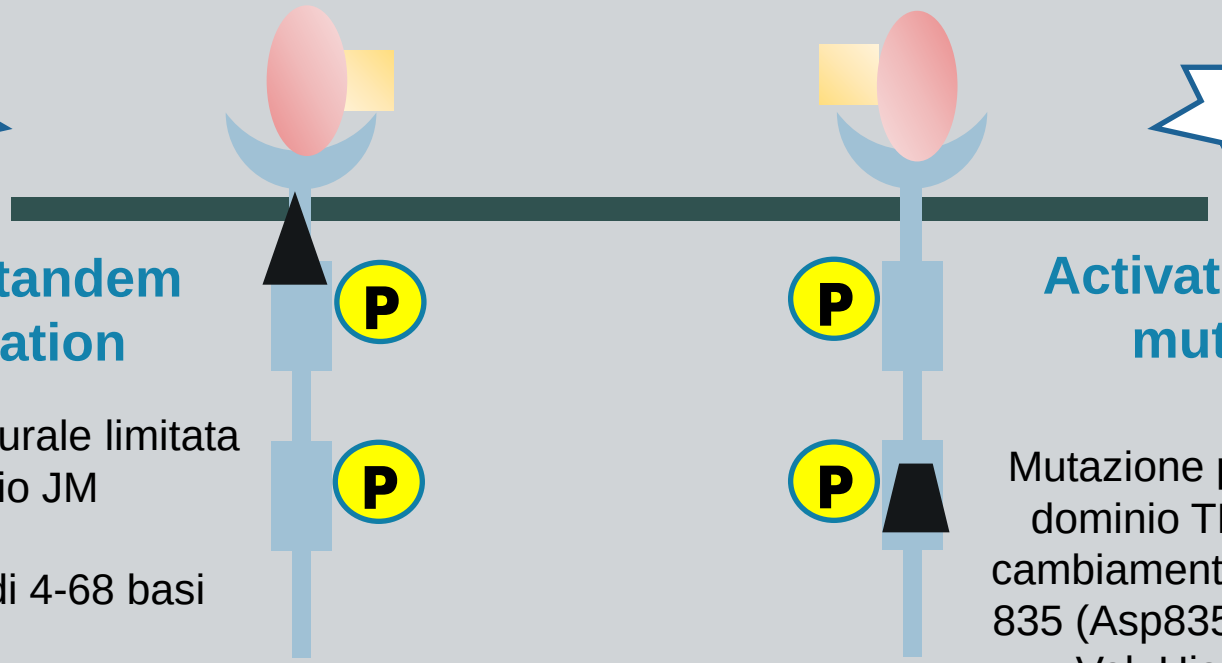
Primariamente espresso sulle cellule empoietiche immature, ed è essenziale per la normale funzione delle cellule staminali



Regolazione della differenziazione, sopravvivenza, proliferazione e apoptosi

FLT3

15-35%



~7%

Internal tandem duplication

Mutazione strutturale limitata al dominio JM

Duplicazione di 4-68 basi

Perdita dell'autoinibizione con passaggio dalla forma inattiva alla forma attiva catalitica senza la presenza del ligando

Activation Loop mutation

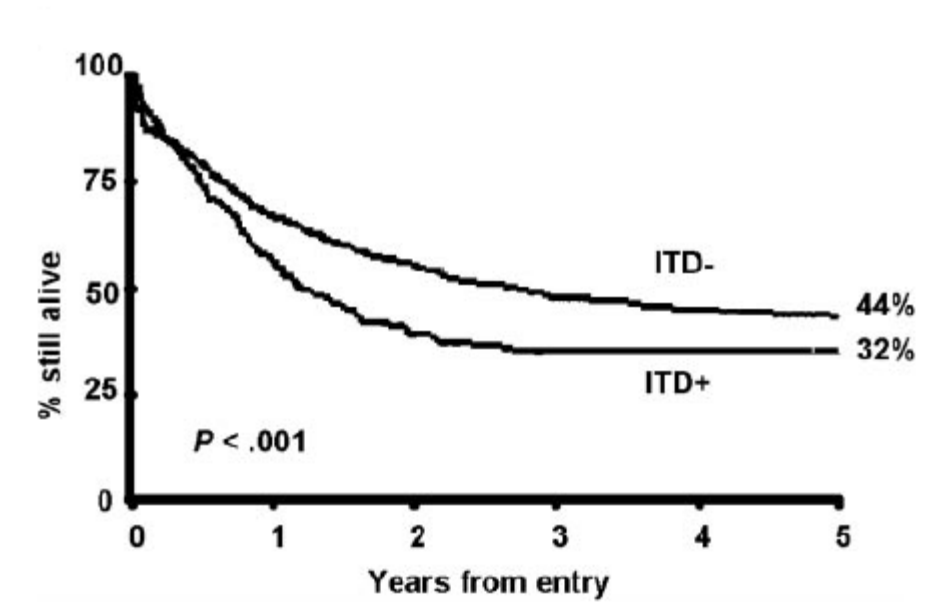
Mutazione puntiforme del dominio TK che induce cambiamento aa al codone 835 (Asp835Tyr, ma anche Val, His, Glu, Asn)

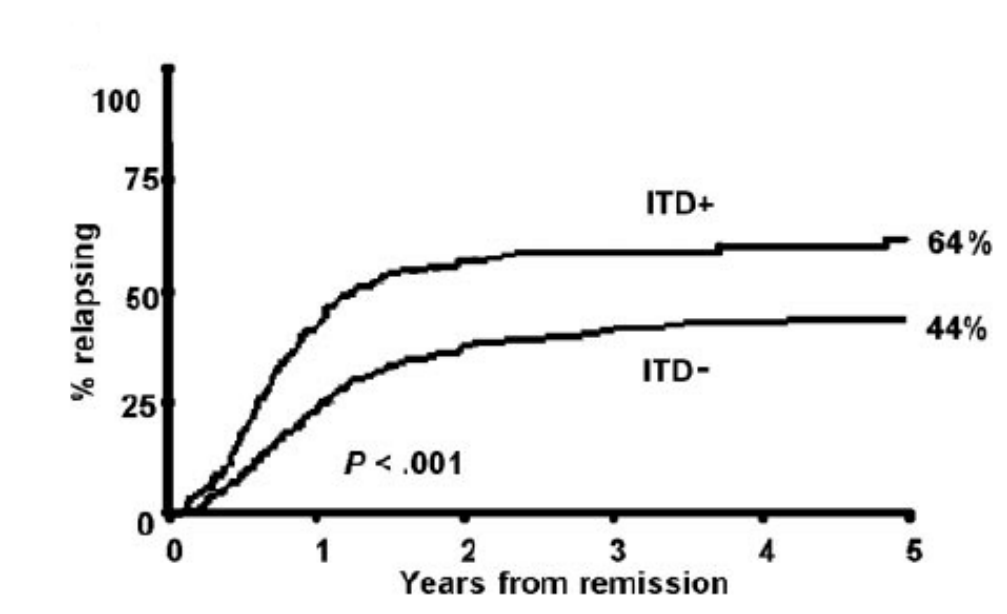
Attivazione costitutiva per autofosforilazione

Prognosi molto neg

Proliferazione cellulare

FLT3





Leucocitosi, elevata percentuale di cellule blastiche nel midollo

Aumentato rischio di recidiva

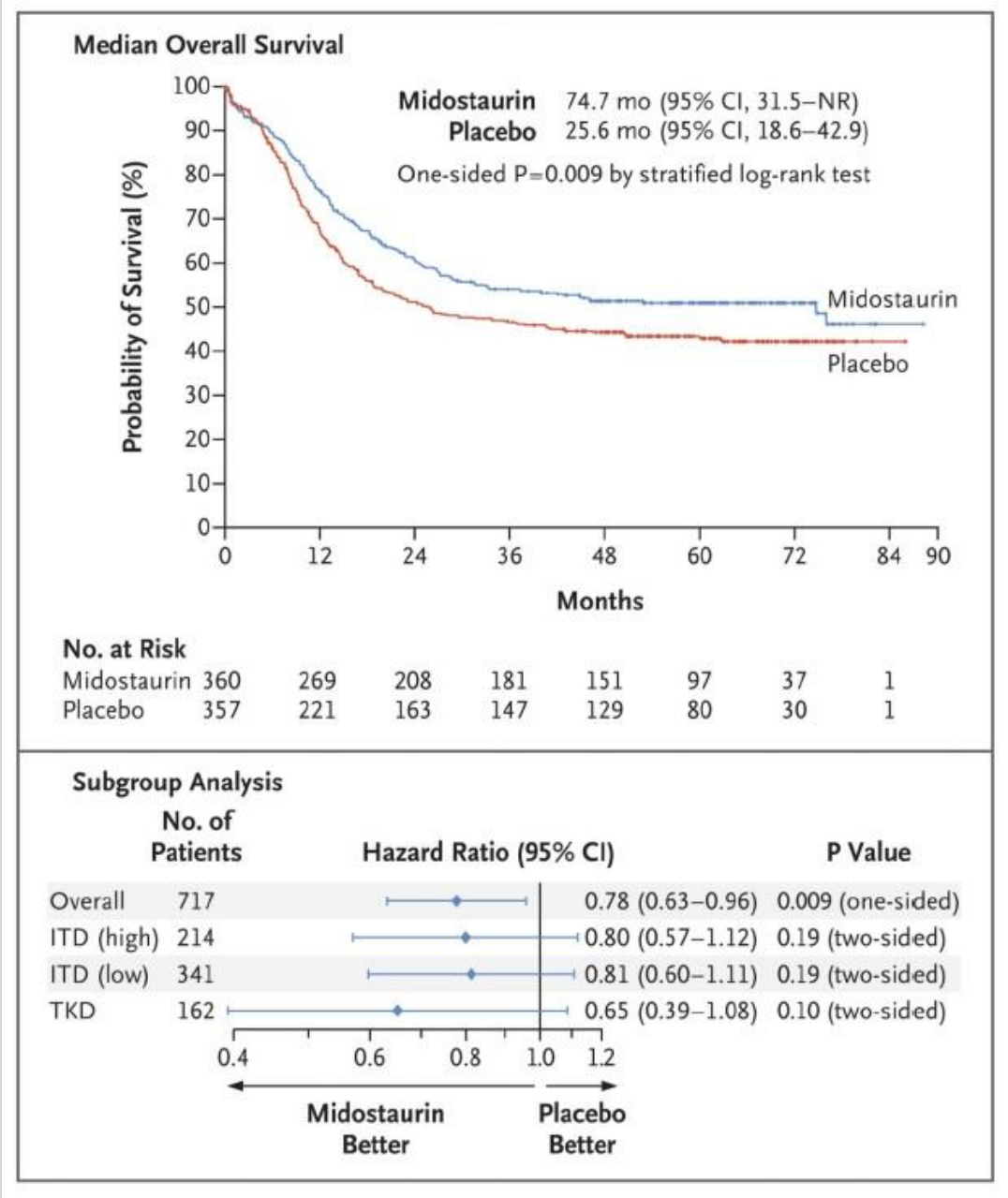
Ridotta sopravvivenza

Panajotis D et al. Blood 2001; 98: 1752

First-generation of FLT3 TKIs

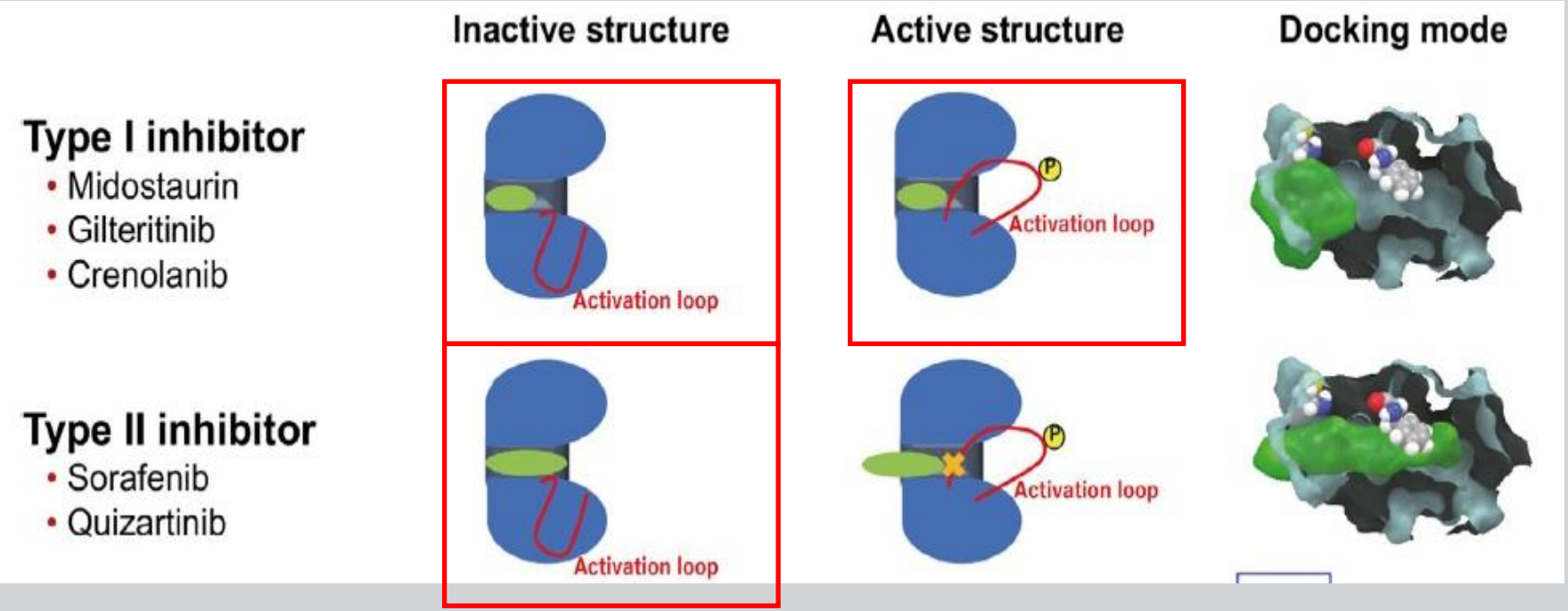
- **Midostaurin**, an oral multi-targeted kinase inhibitor with activity against activated FLT3 (ITD and TKD).
- Added to intensive induction and consolidation therapy followed by 1-year maintenance in de novo FLT3 AML (not as monotherapy).
- 22% lower risk of death with the addition of midostaurin to standard chemotherapy (RATIFY study).

Significant improvement in OS (median OS 74.7 vs 25.6 months, P = 0.009) and EFS (8.2 months vs. 3 months)



RATIFY study. Stone RM et al. N Engl J Med. 2017

FLT3 TKIs



OBJECTIVE: prevent/treat resistance mechanisms

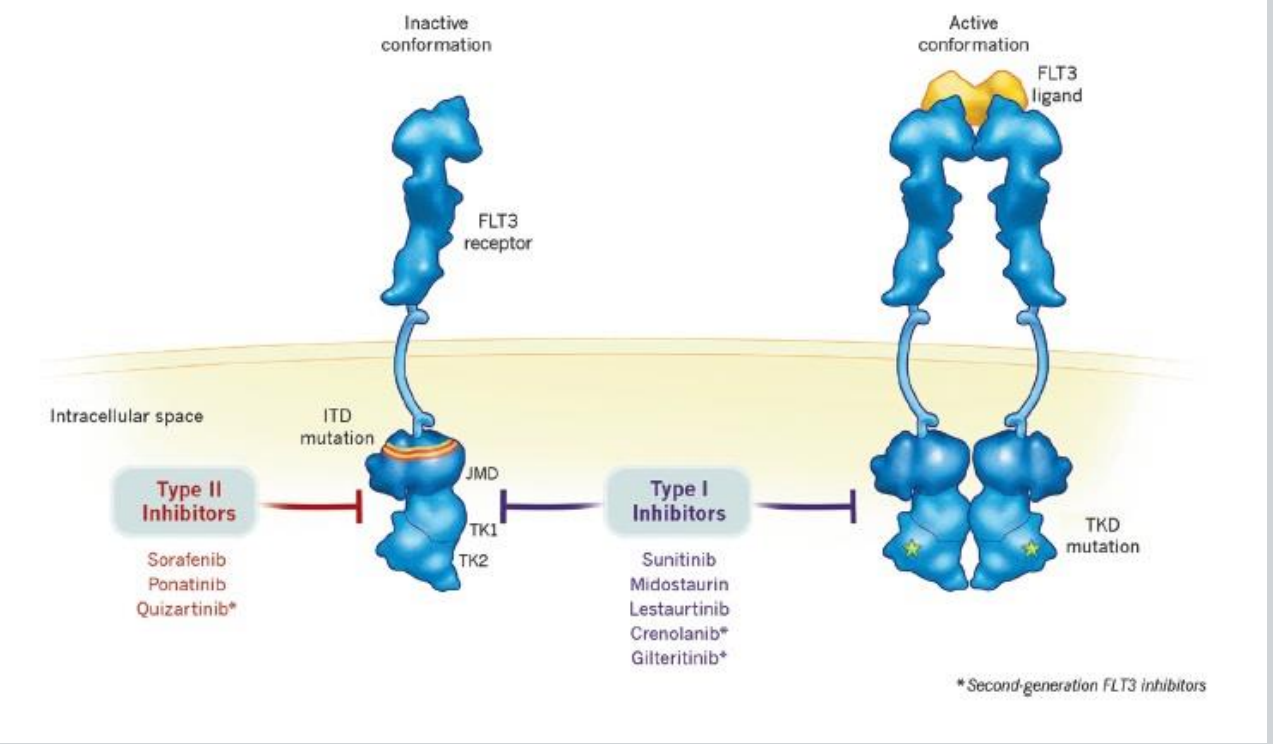
Type I inhibitors show potency against multiple kinases

Type II with more selective and potent inhibitory activities

FLT3 TKIs: mechanisms of action

Type II

- ❑ FLT3 receptor in the inactive conformation
- ❑ Region adjacent to the ATP binding domain
- ❑ Active against ITD mutation



Type I

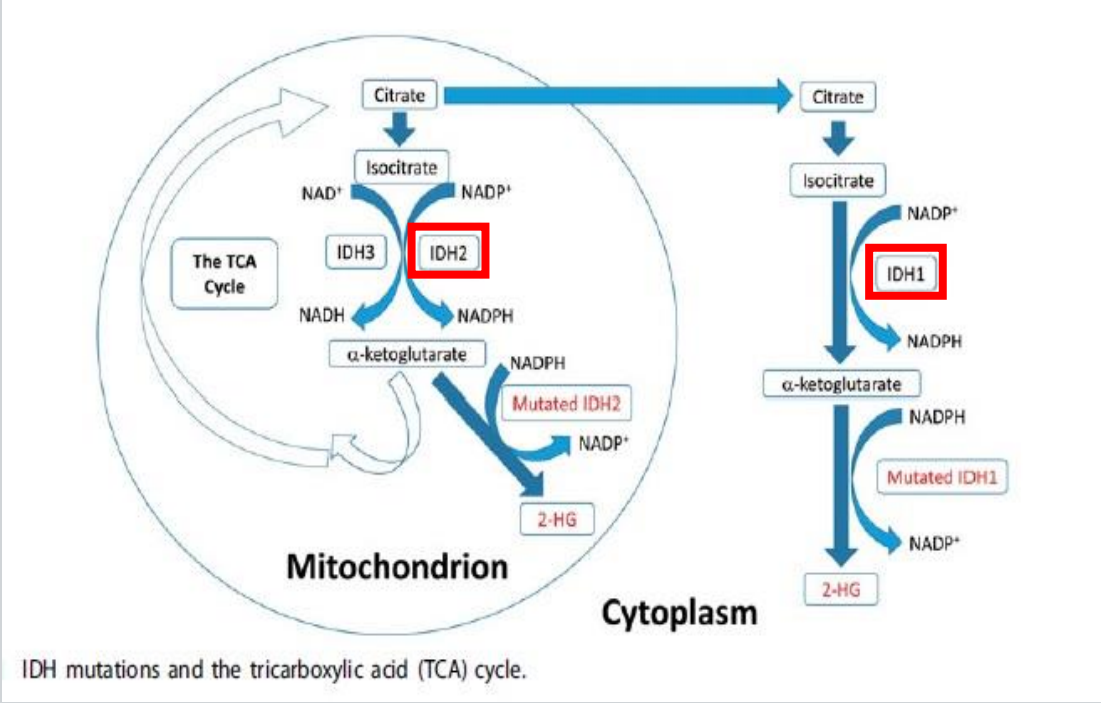
- ❑ FLT3 receptor in the active conformation
- ❑ Activation loop or the ATP binding pocket
- ❑ Active against ITD and TKD mutations

INIBITION OF CELL PROLIFERATION

IDH

Isocitrate dehydrogenase (IDH) mutations

- **Occur in 20% of AML patients. Generally mutually exclusive. Prognostic implications are complex and controversial.**
- **Affect specific arginine residues (IDH1 R132 and IDH2 R140 or R172), are typically heterozygous, and are somatically acquired.**
- **Early events in leukemogenesis that tend to be stable, presenting again at the time of possible relapse.**



IDH mutations and the tricarboxylic acid (TCA) cycle.

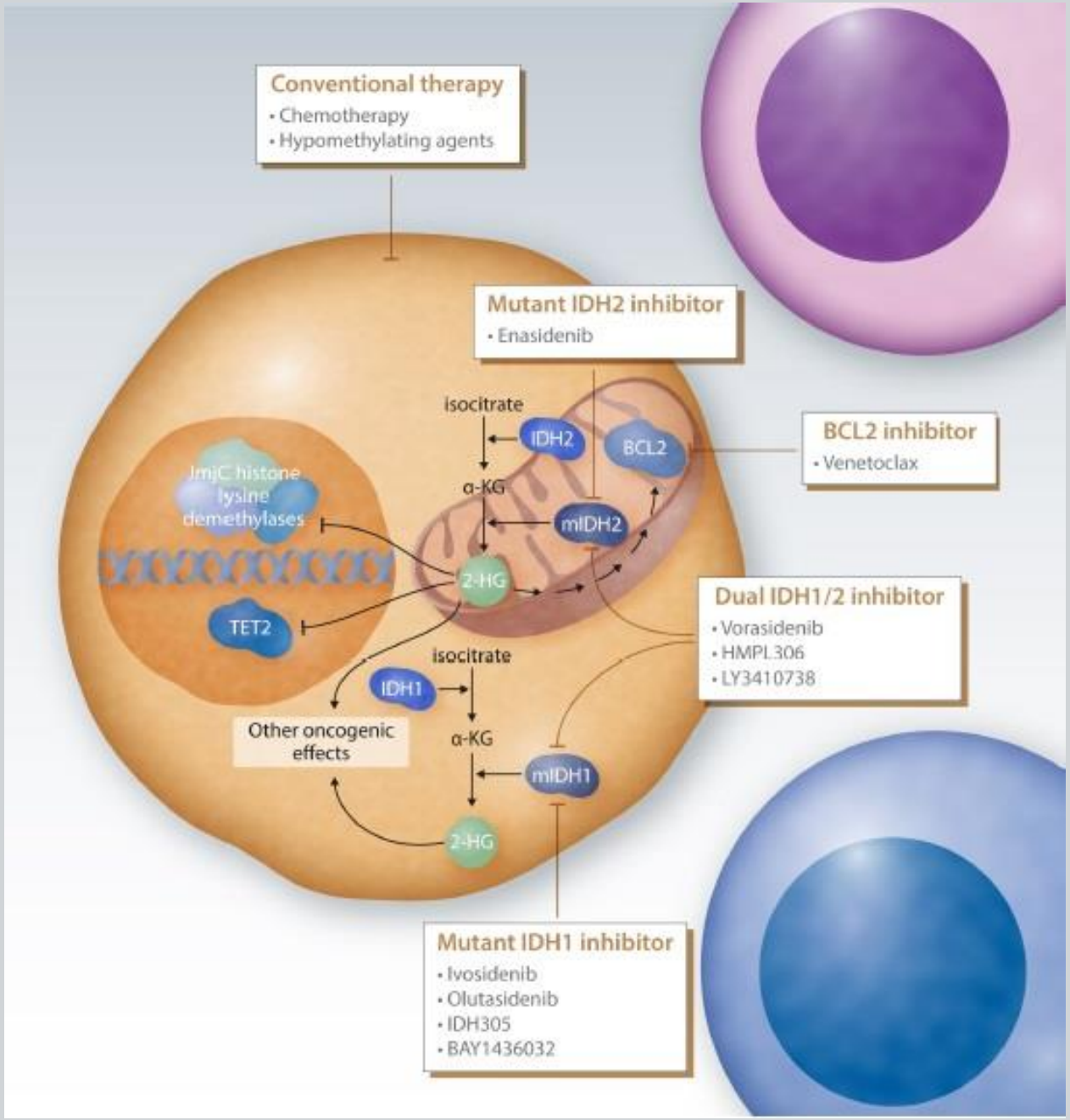
Increased production of 2 hydroxyglutarate (2-HG) and epigenetic modification, affecting cell differentiation.

IDH

IDH-mutated AML is characterized by a genome-wide increase in DNA hypermethylation and a block of myeloid differentiation

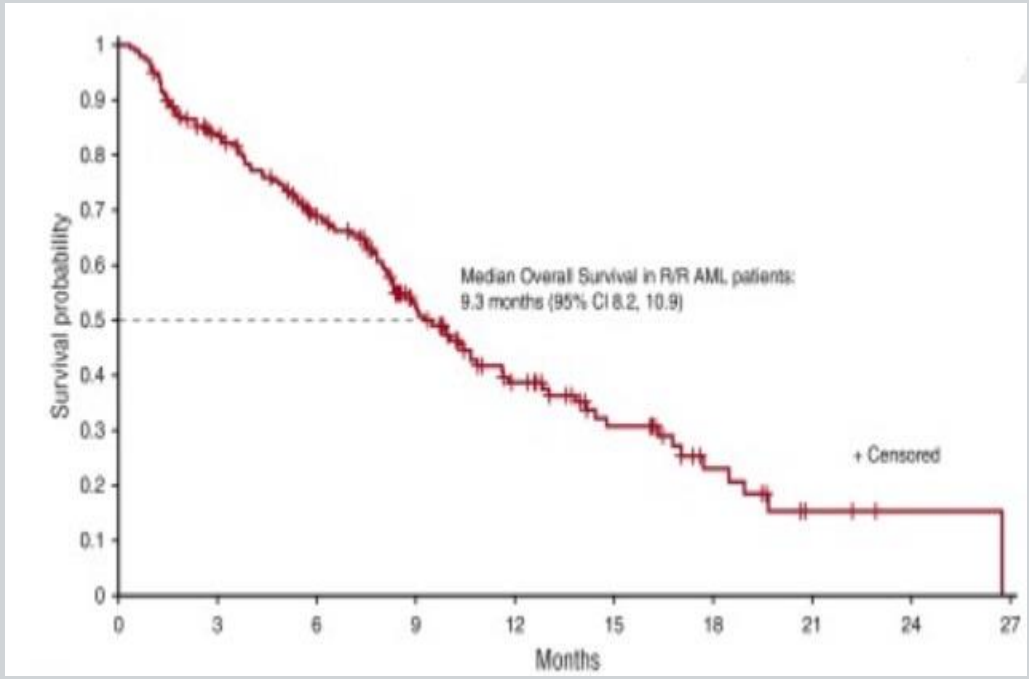
- **IDH inhibitors selectively inhibit mutant IDH proteins and block the aberrant production of 2-HG.**

Myeloid differentiation induced



IDH inhibitors

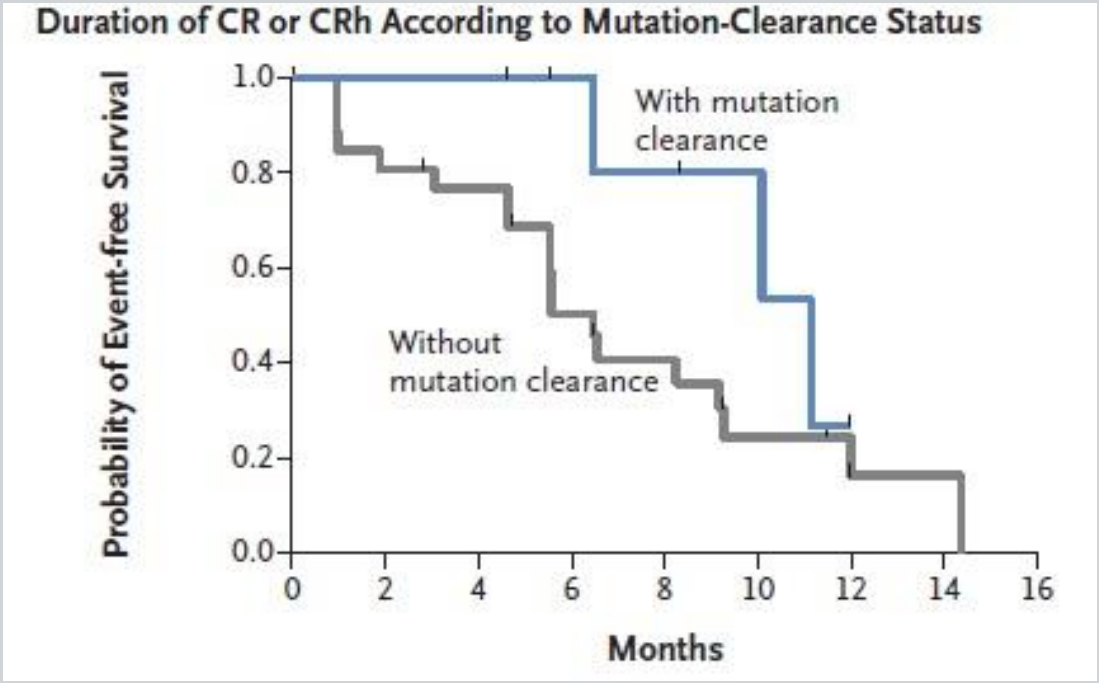
IDH2 inhibitor enasidenib



OS 38.8%
median OS 8.8 months
CR 28.9%

Stein EM et al. Blood 2017

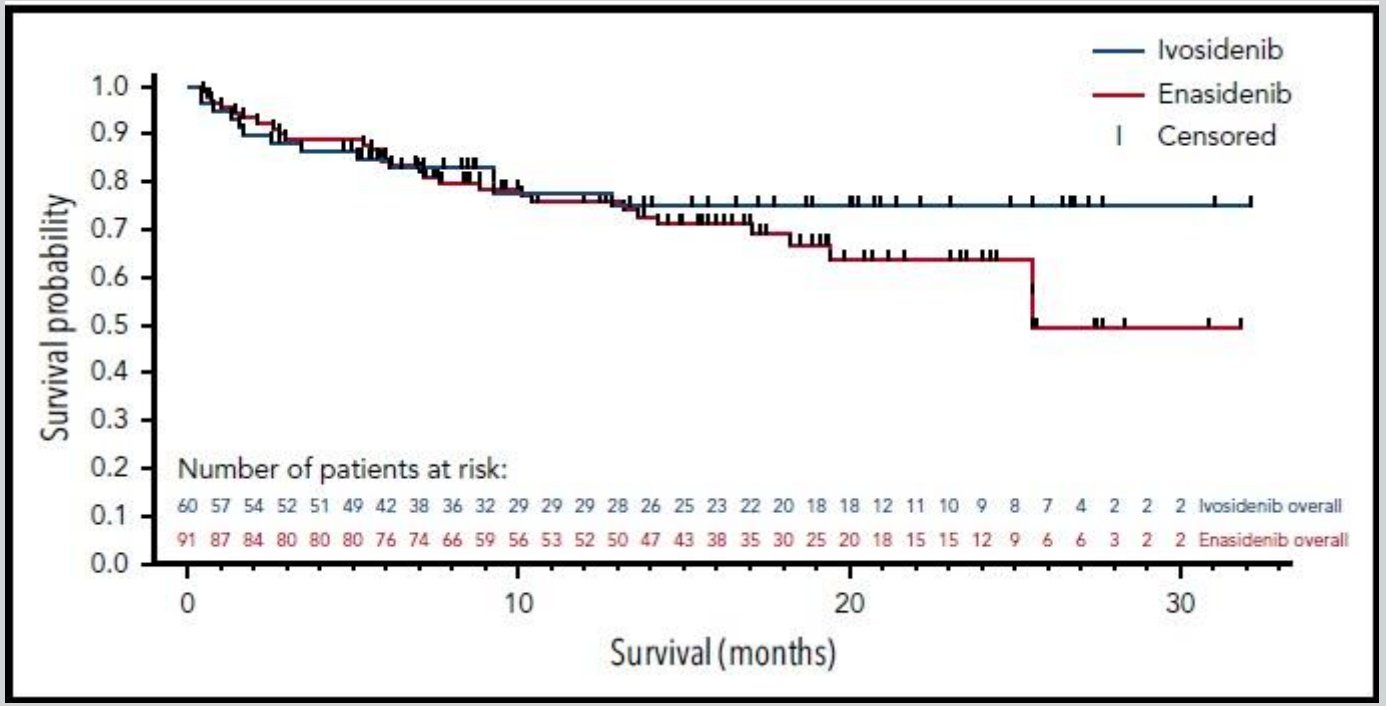
IDH1 inhibitor ivosidenib



OS 41.6%
median OS 8.8 months
CR 34.4%

DiNardo CD et al. N Engl J Med. 2018

IDH inhibitors with chemoterapy



- **Ivosidenib or enasidenib combined with induction and consolidation chemotherapy** were both well tolerated in newly diagnosed mutated IDH1/2 AML.
- CR rates: 77% (ivosidenib) and 74% (enasidenib); 39% and 23% of patients had IDH1/2 mutations clearance by dPCR.

Stein EM et al. Blood 2021