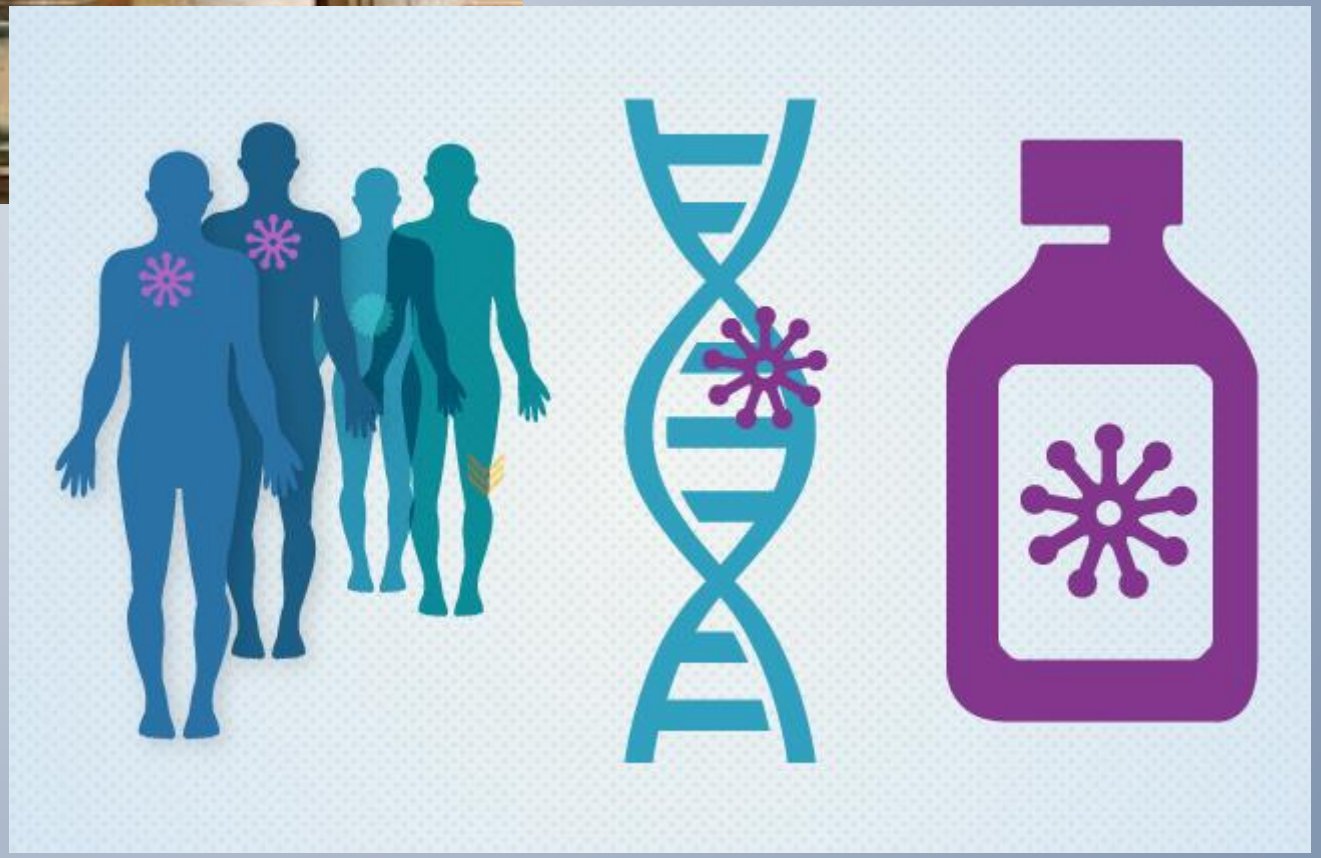
Evoluzione della terapia in oncoematologia: dalla chemioterapia alla terapia target

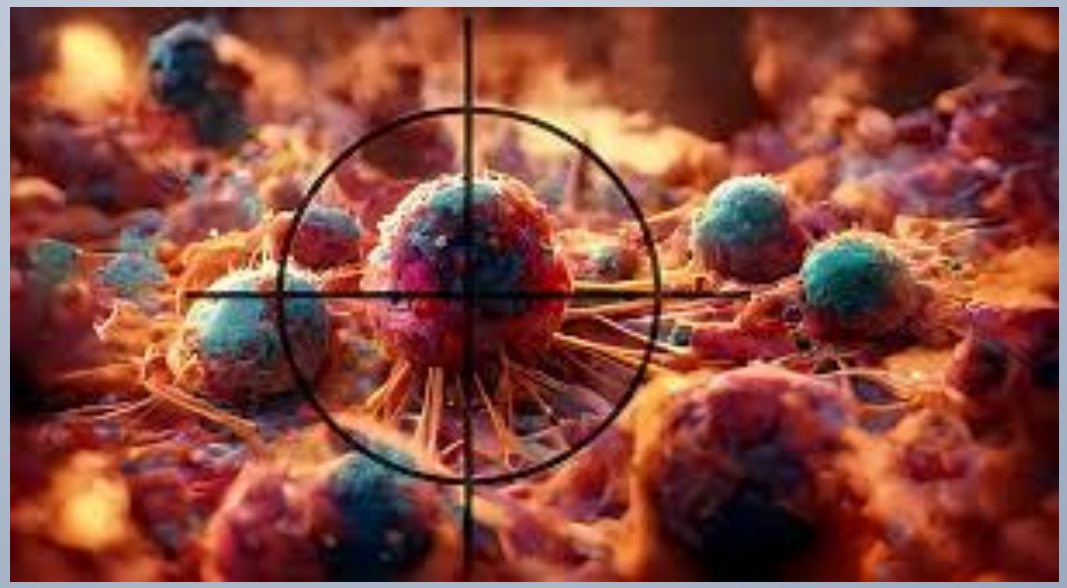
Dr.ssa Simona Bernardi


Tinctura
Ginsquiam



Agenda

- BCR::ABL1 as TKIs and asciminib target
- JAK2 mutated as target of ruxolitinib
- PML-RARalpha as target of ATRA therapy
- FLT3-ITD and IDH2 mutated as target of target therapy in AML



CHRONIC MYELOID LEUKEMIA

BCR::ABL1 as target of TKIs therapy and asciminib

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

BCR::ABL1 :

ABL1: Tyrosyn-kinase with enzimatic activity.

BCR: serin/treonyn kinase with a key role in the signal transduction.

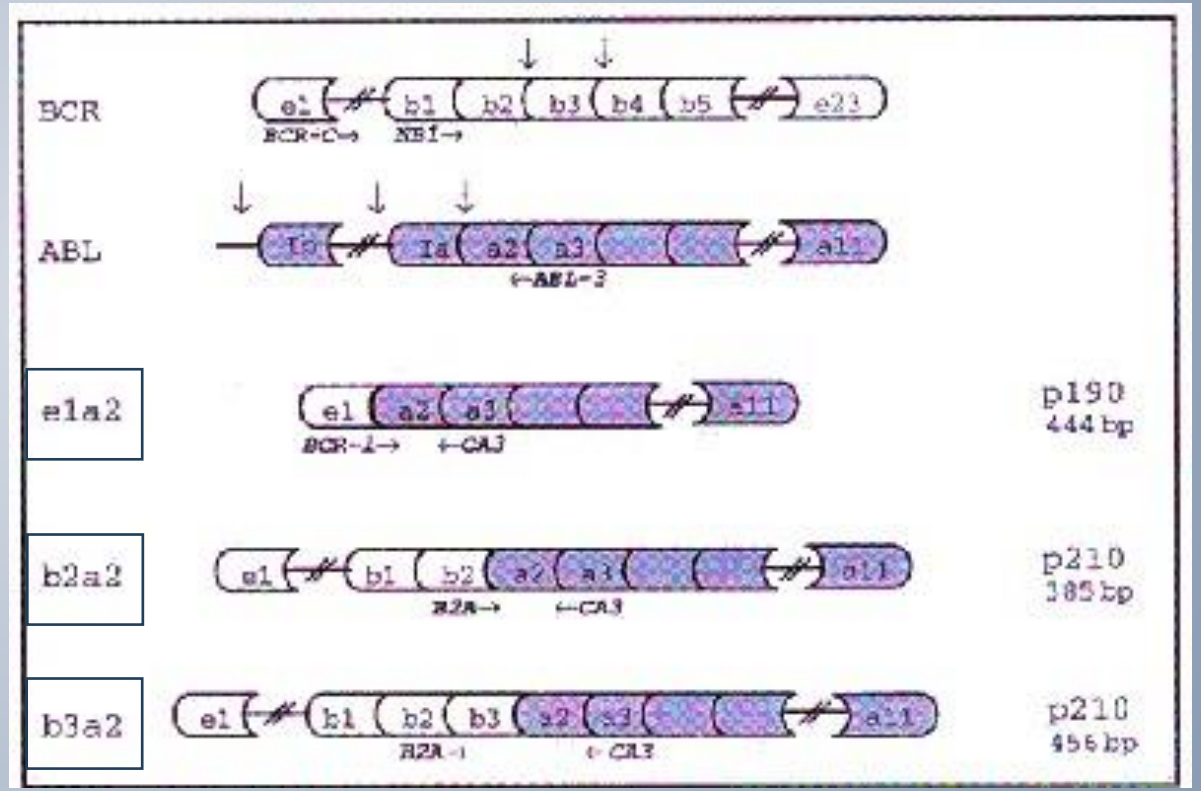
t(9;22)(q34;q11.2)

Chimeric protein isoforms

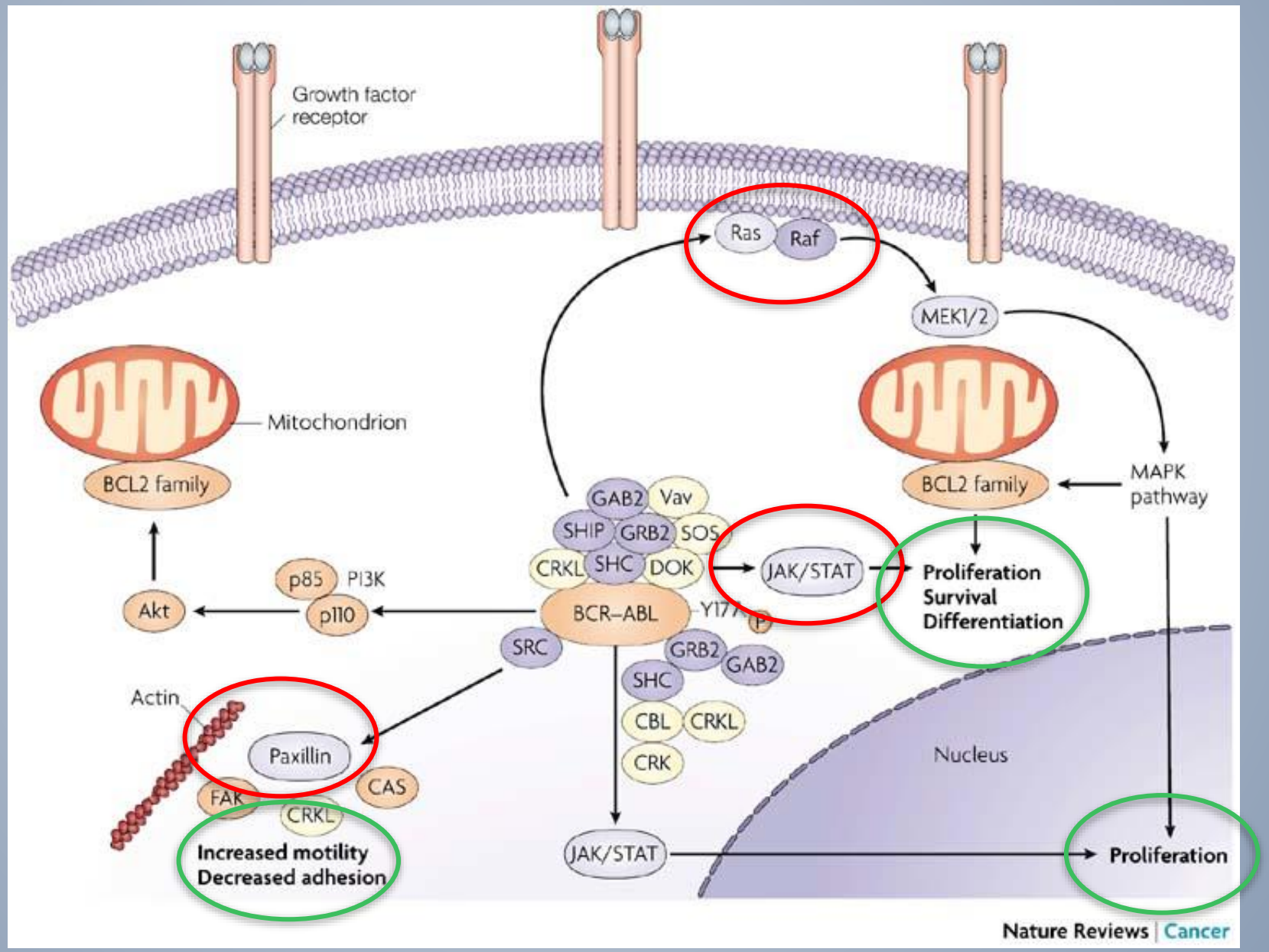
p190 (LAL)

p210 (CML, raramente LAL)

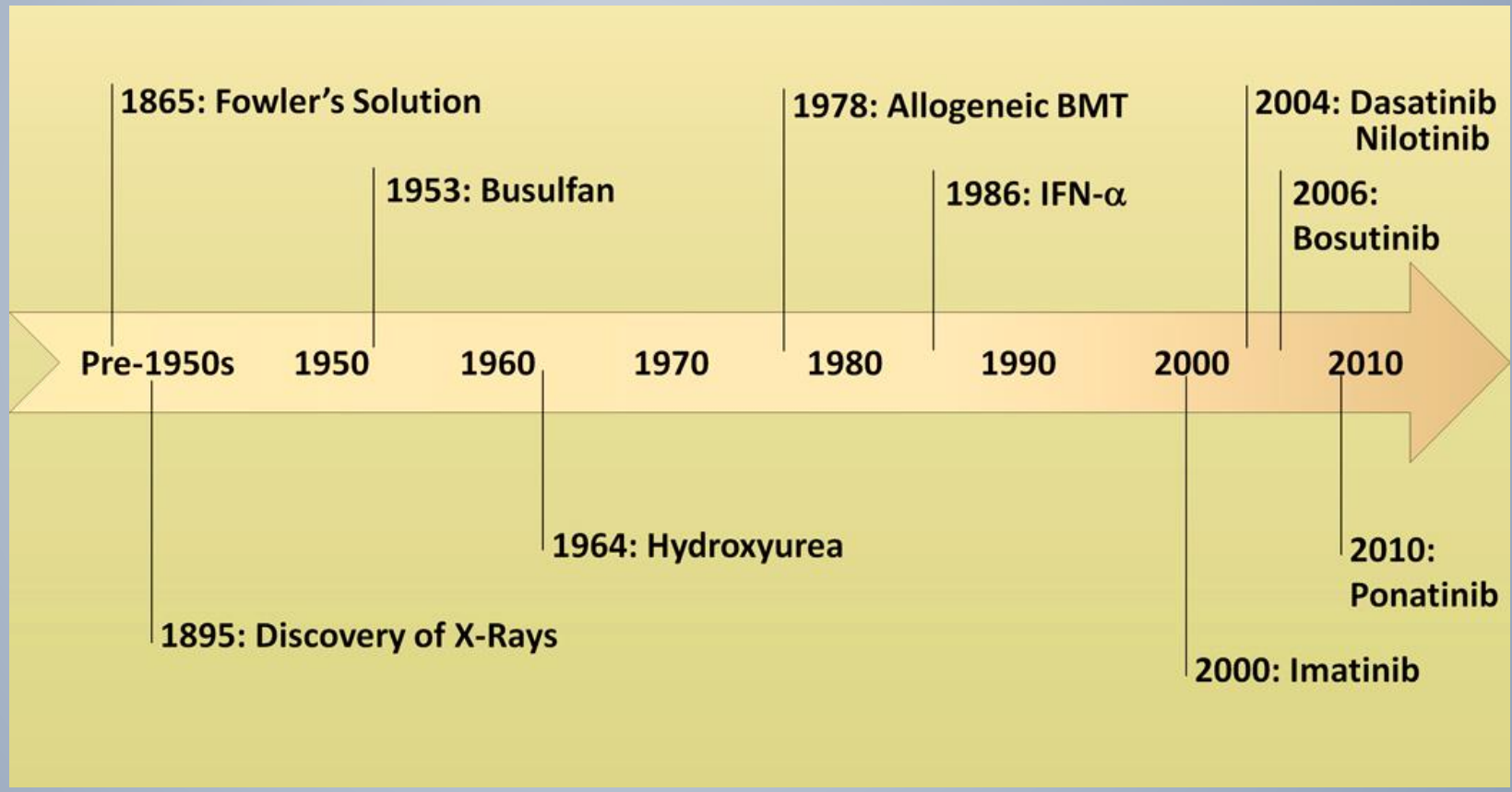
p230 (CML)



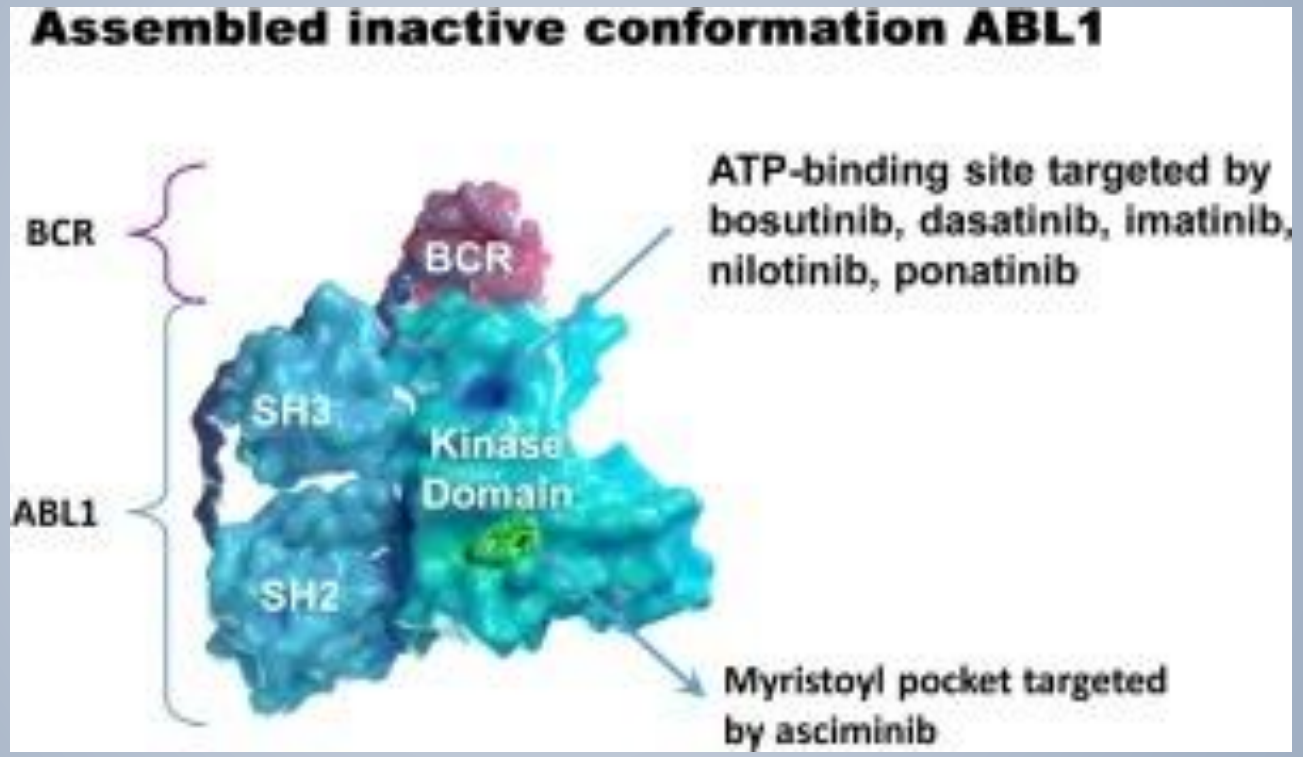
t(9;22)(q34;q11.2)

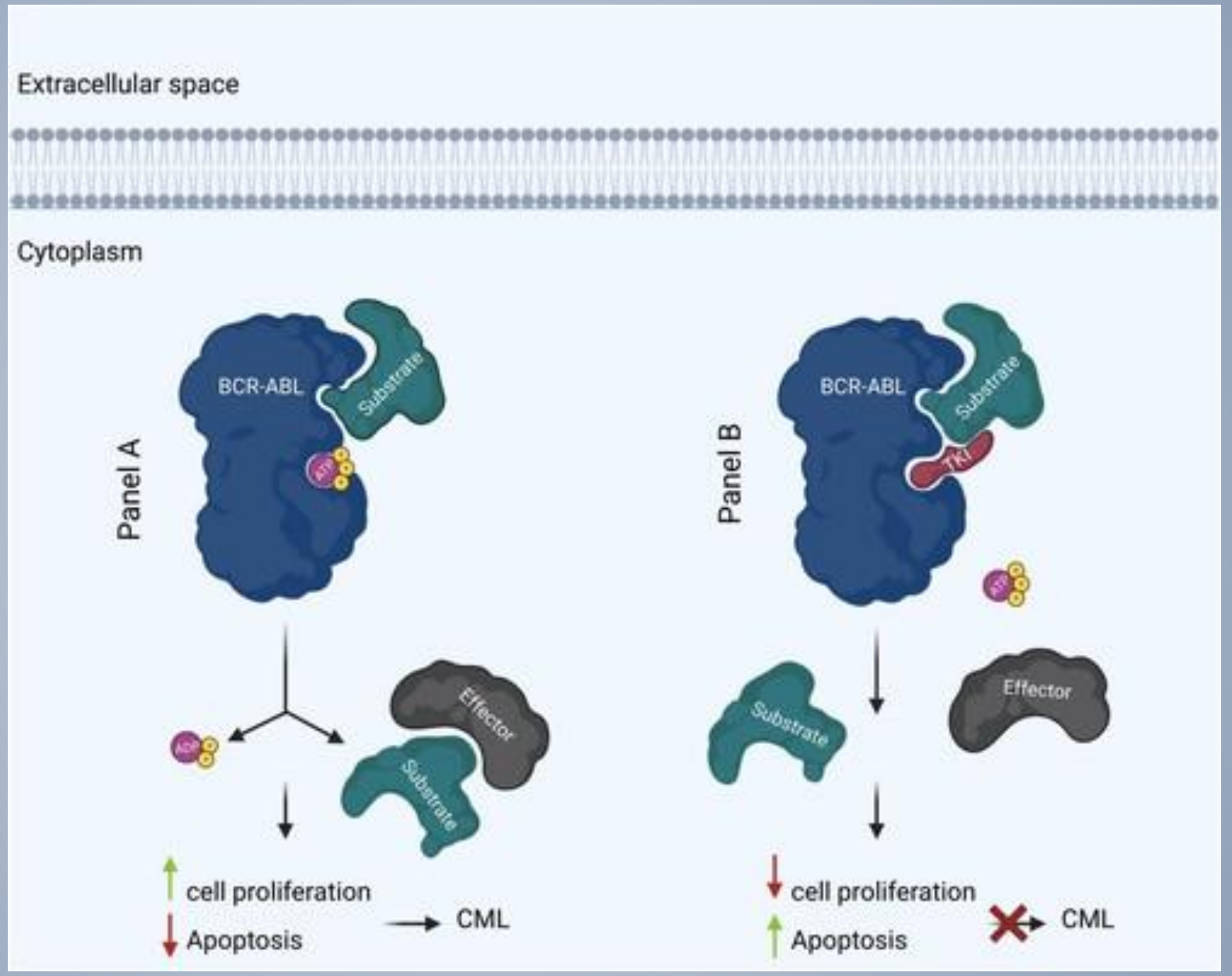


Evolution of the therapy in CML



The TKIs


Assembled inactive conformation ABL1
BCR
ABL1
BCR
SH3
Kinase Domain
SH2
ATP-binding site targeted by bosutinib, dasatinib, imatinib, nilotinib, ponatinib
Myristoyl pocket targeted by asciminib


Extracellular space
Cytoplasm
Panel A
BCR-ABL
Substrate
ATP
Effector
Substrate
cell proliferation
Apoptosis
CML
Panel B
BCR-ABL
Substrate
TKI
ATP
Substrate
Effector
cell proliferation
Apoptosis
CML

Different generation of TKIs

- More potent
- Higher efficacy
- More toxic
- Active also against other kinases

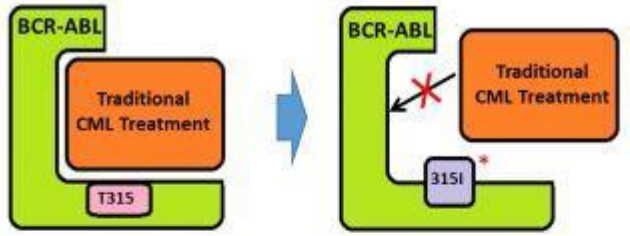
TKI	Specificity of TKI	MMR	DMR	Changes to Another TKI	OS, PFS	Side Effect
Imatinib (IM)	1G TKI the first choice for the treatment of CML	20–59%/1 years 60–80%/5 years	MR4 or deeper: 35–68%/5 years	37% [a] and 50% [b]/5 years 26.5% [c]/10 years	OS: 90–95%/5 years 82–85%/10 years PFS: 80–90%/5 years 6% leukemia-related death rate [c,d]	no life-threatening complications [c,d] early fluid retention, gastrointestinal symptoms, muscle cramps, joint pain, skin rash, fatigue [e]
Nilotinib (NIL)	2G TKI active against *BCR-ABL1* mutants: V299L, F317L/V/I/C, T315A	77% [b]/5 years 82.6% [f]/10 years 98% [g]/10 years	MR4: 66%/5 years 73%/10 years 76% [g]/10 years MR4.5: 54%/5 years 64%/10 years	40%/10 years	OS: 94%/5 years 87.6%/10 years 94% [g]/10 years	cardiovascular events [h] pancreatitis [b,f,g]
Dasatinib (DASA)	2G TKI active against *BCR-ABL1* mutants: Y253H, E255V/K, F359V/I/C	46% [a]/1 year 76% [a]/5 years	MR4.5: 42%/5 years	39%/5 years	OS: 91%/5 years PFS: 86%/5 years	pleuro-pulmonary toxicity recurrent pleural effusions rarely pulmonary arterial hypertension [a]
Bosutinib [i] (BOS)	2G TKI active against *BCR-ABL1* mutants: Y253H, E255V/K, F359V/I/C, F317L/V/I/C, T315A	47% [j]/1year	NR	NR	NR	transient diarrhea transient elevations of transaminases [k]

BCR::ABL1 (IS)	3 months	6 months	12 months[a]
> 10%	YELLOW	RED	
> 1% – 10%	GREEN		YELLOW
> 0.1% – 1%	GREEN		LIGHT GREEN
≤ 0.1%	GREEN		

Color	Concern	Treatment Team Considerations	Recommendations
RED	TKI-resistant disease	• Evaluate patient adherence and drug interactions • Consider mutational analysis	• Switch to alternate TKI • Evaluate for allogeneic stem cell transplantation
YELLOW	Possible TKI resistance	• Evaluate patient adherence 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) ***OR*** • Dose escalation of imatinib (to a max of 800 mg) ***AND*** • Consider evaluation for allogeneic stem cell transplantation
LIGHT GREEN	TKI-sensitive disease	• If treatment goal is long-term survival: ≤1% optimal • If treatment goal is treatment-free remission: ≤0.1% optimal	• If optimal: continue same TKI • If not optimal: shared decision-making with patient[b]
GREEN	TKI-sensitive disease	• Monitor response and manage side effects	• Continue same TKI[c]

Ponatinib

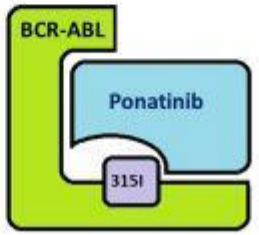
[Traditional Treatment (TKI) and Treatment Resistance due to Mutation]



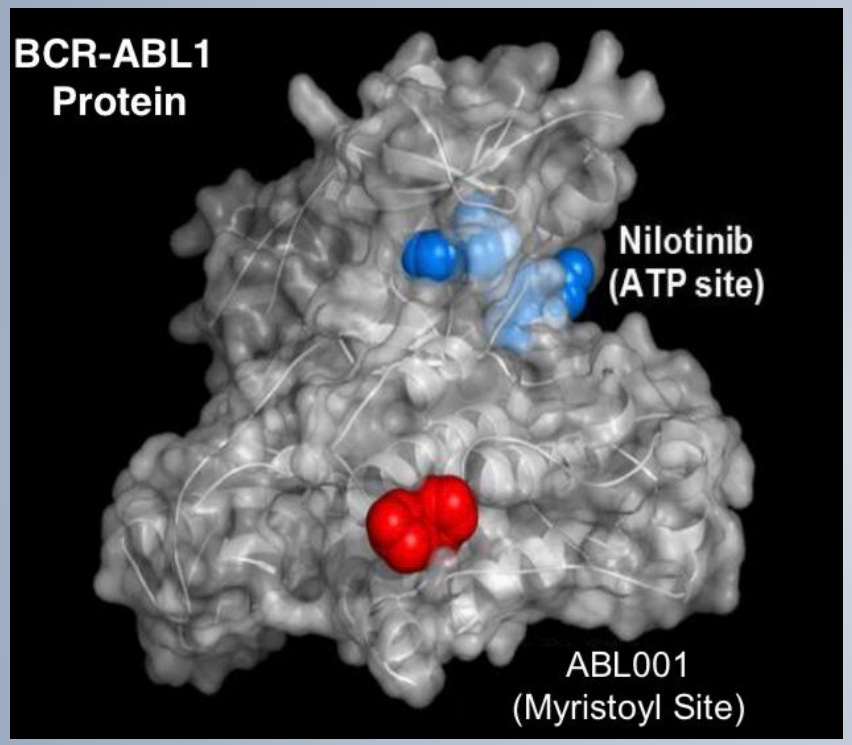
* T315I mutation: The 315th amino acid changes from threonine (T) to isoleucine (I)
If a T315I mutation occurs, traditional treatment (TKI) cannot bind to BCR-ABL and cannot elicit efficacy

[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.



Asciminib

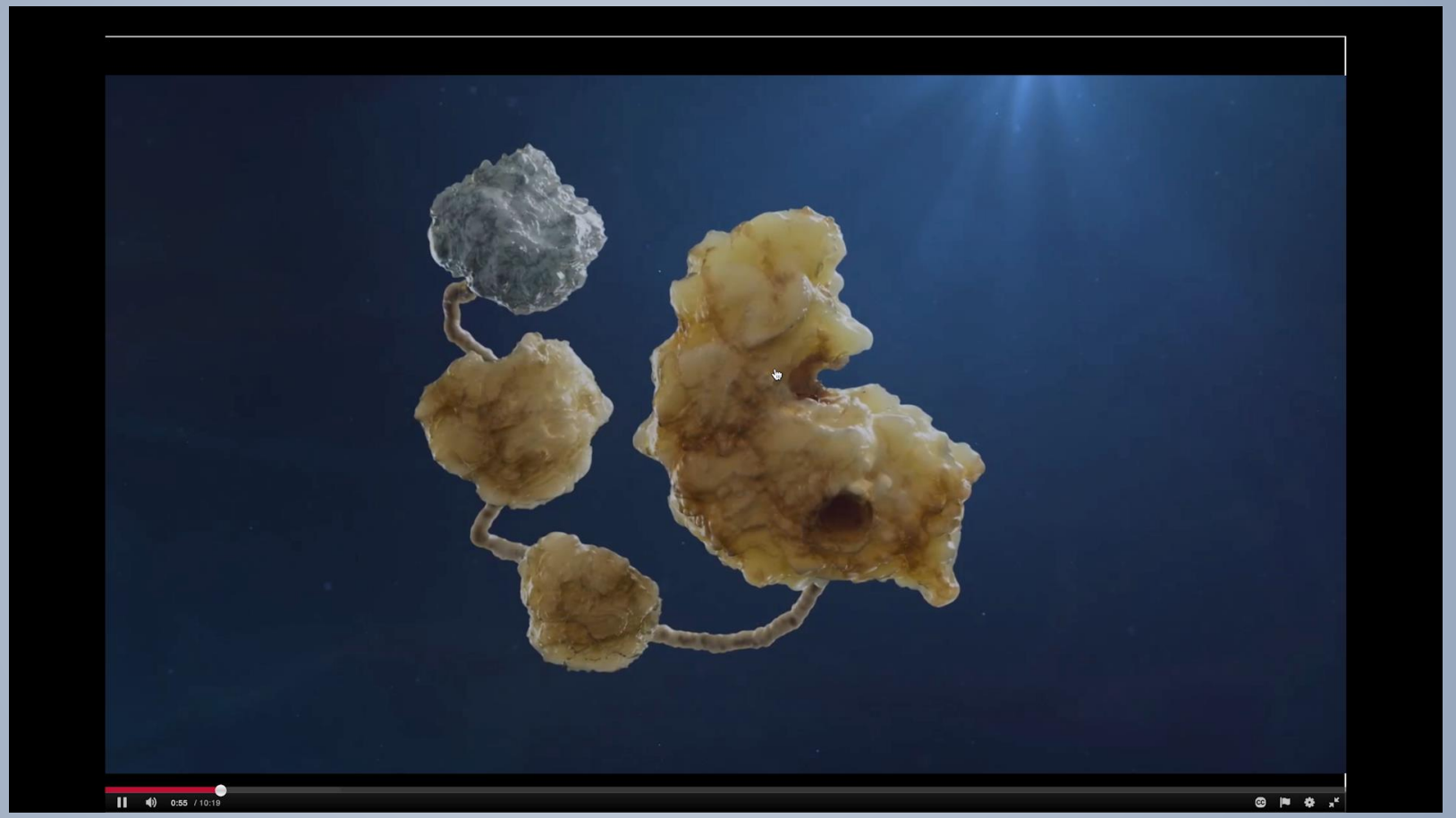


Mechanism of Action

SCEMBLIX (asciminib) WORKS DIFFERENTLY THAN ATP-COMPETITIVE TKIS1

Asciminib is the first and only inhibitor that binds to the ABL myristoyl pocket. The myristoyl pocket is a distinct site of the kinase domain, normally occupied by the myristoylated N-terminal of ABL1 in people who do not have CML.

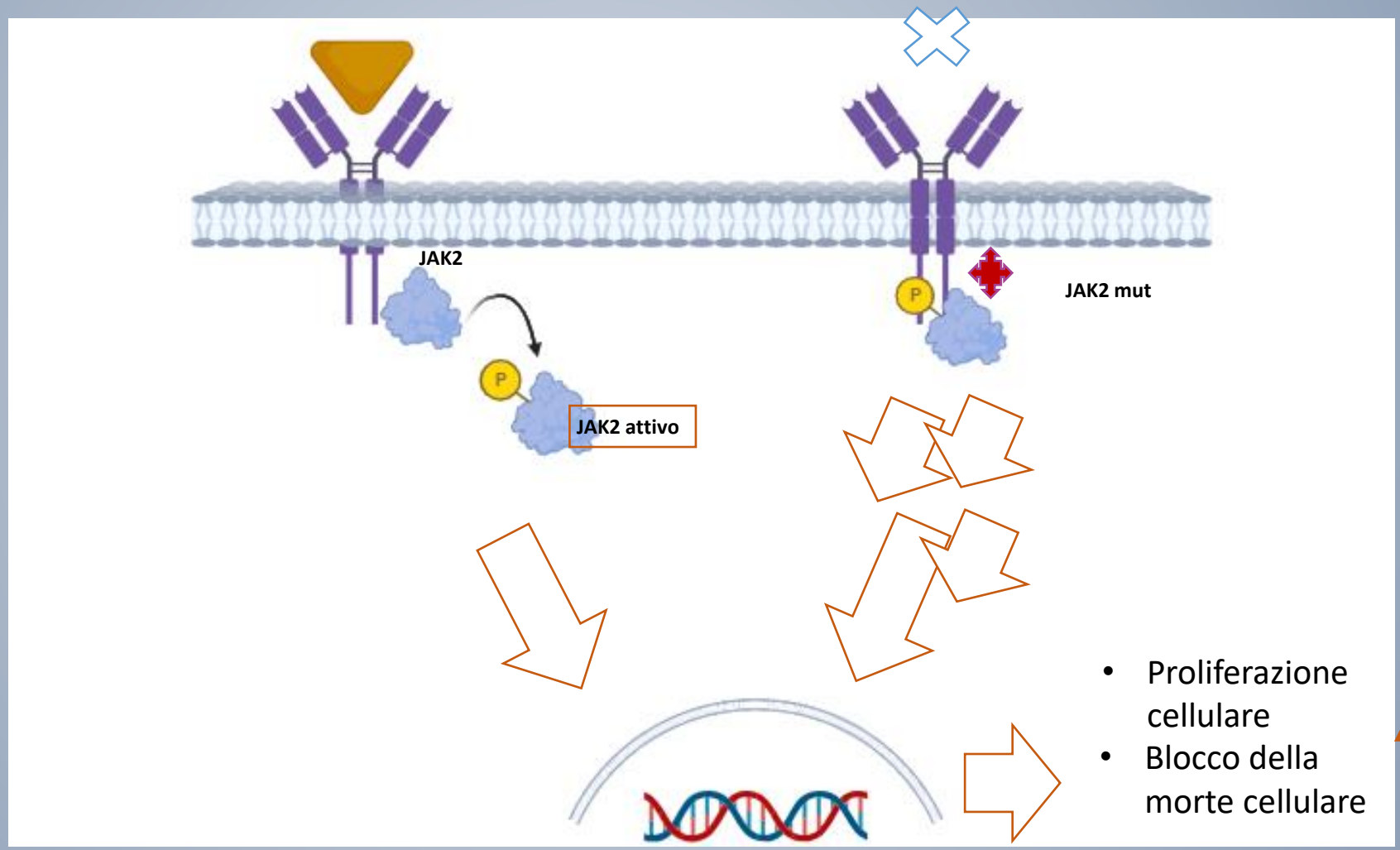
In studies conducted in vitro or in animal models of CML, SCEMBLIX showed activity against wild-type BCR::ABL1 and several mutant forms of the kinase, including the T315I mutation


0:55 / 10:19

MPNs

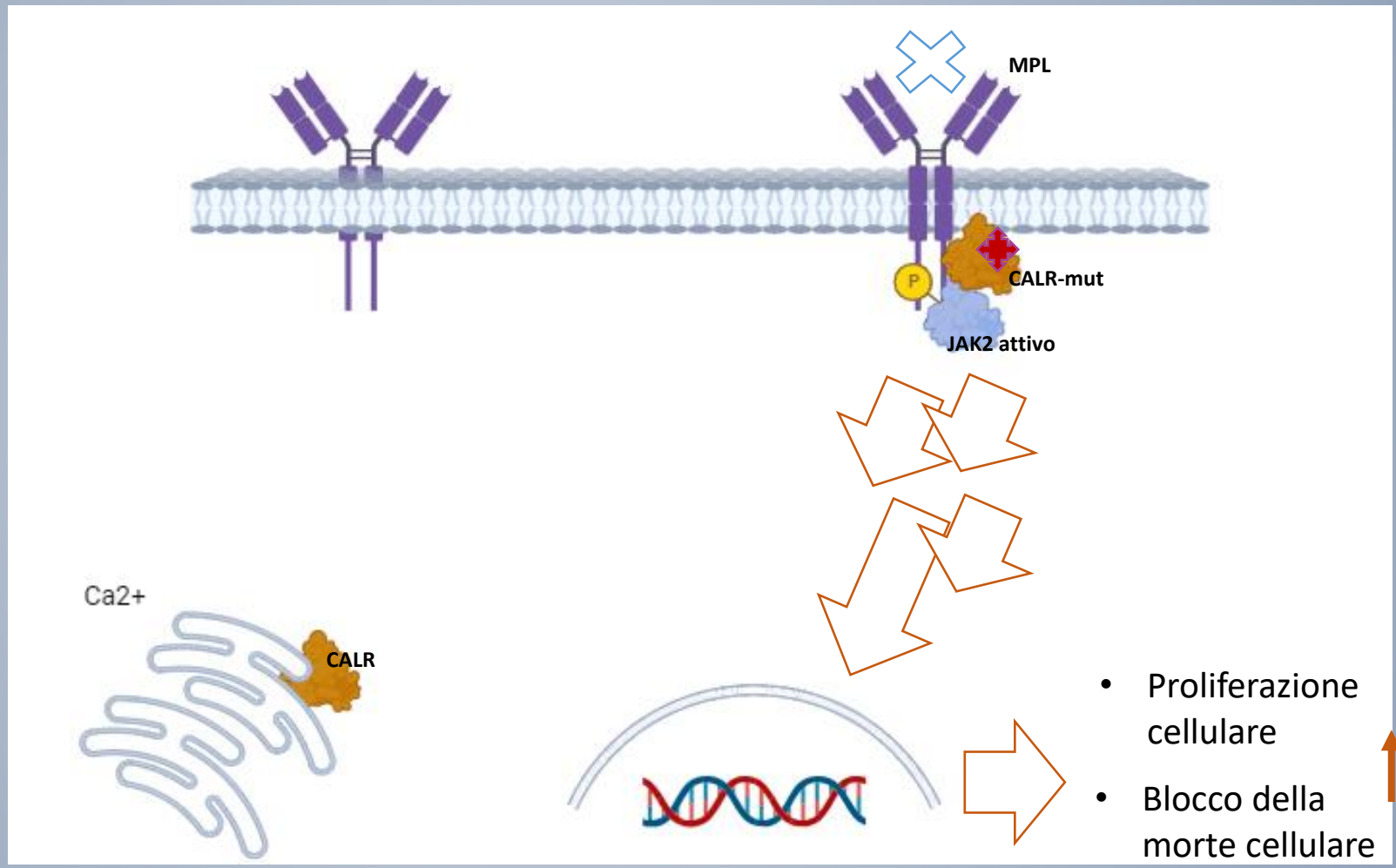
Mutated JAK2 as target of ruxolitinib

JAK2



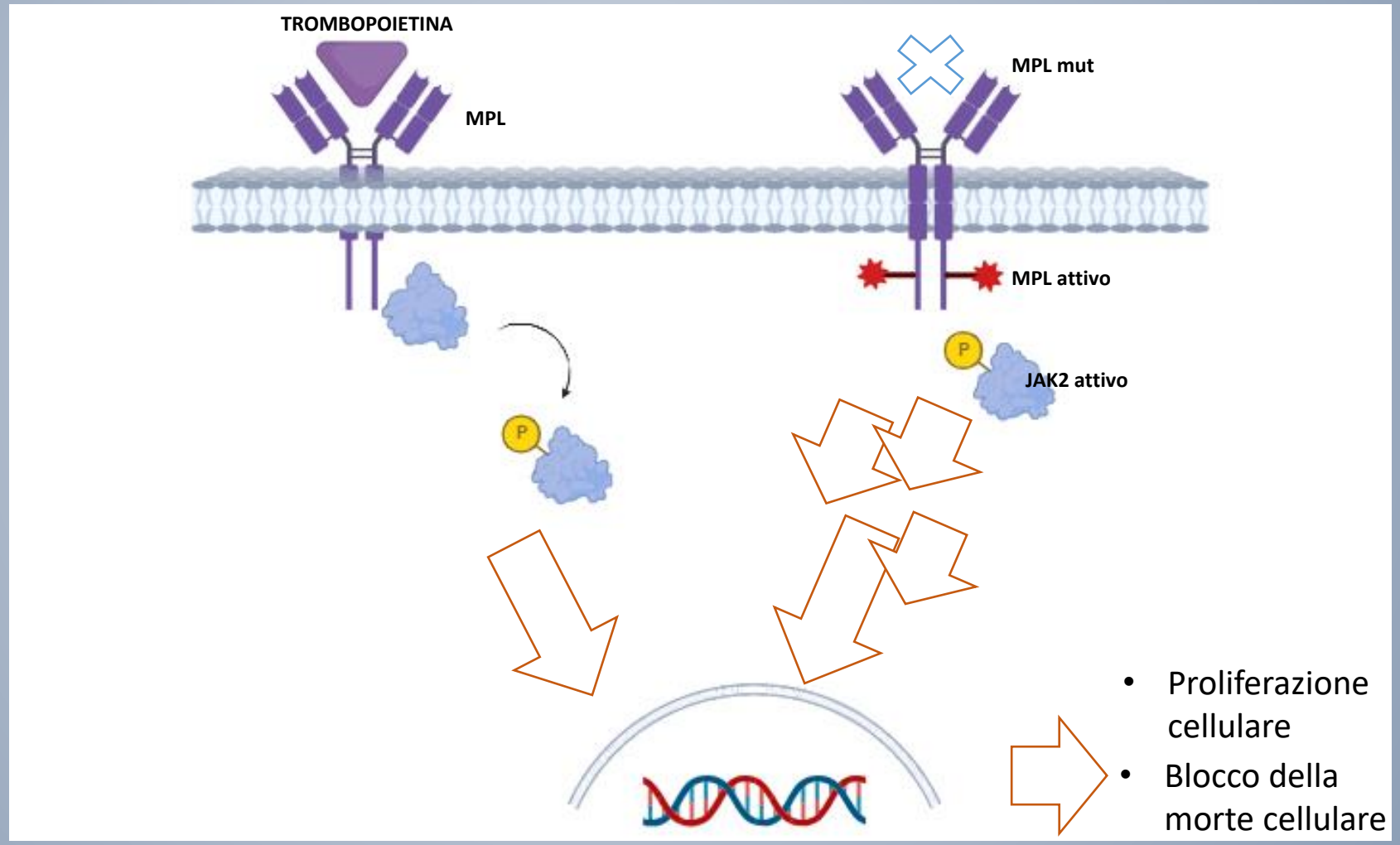
- Proliferazione cellulare
- Blocco della morte cellulare

CALR



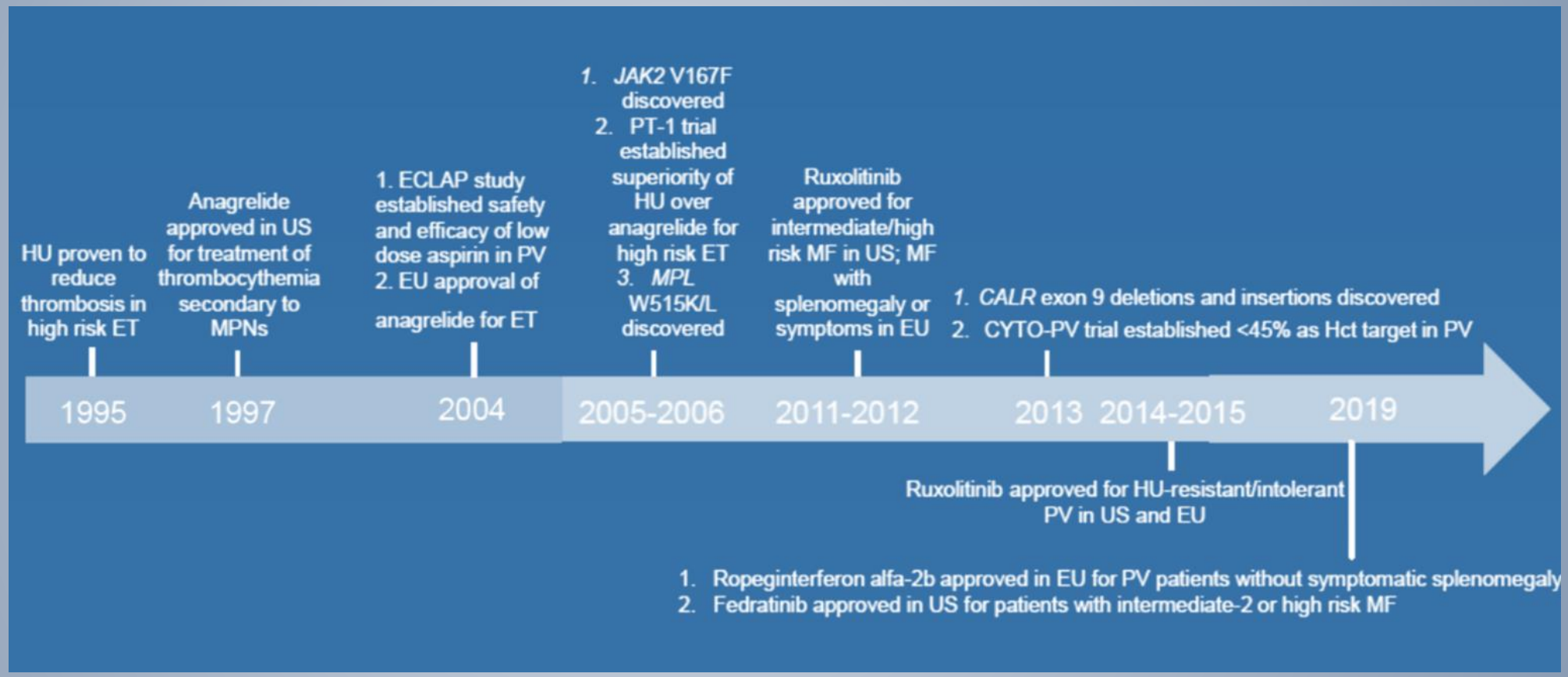
- Proliferazione cellulare
- Blocco della morte cellulare

MPL



- Proliferazione cellulare
- Blocco della morte cellulare

Evolution of the therapy in MPN



Different JAK Inhibitors

Clinical Development of JAKi therapies in MF

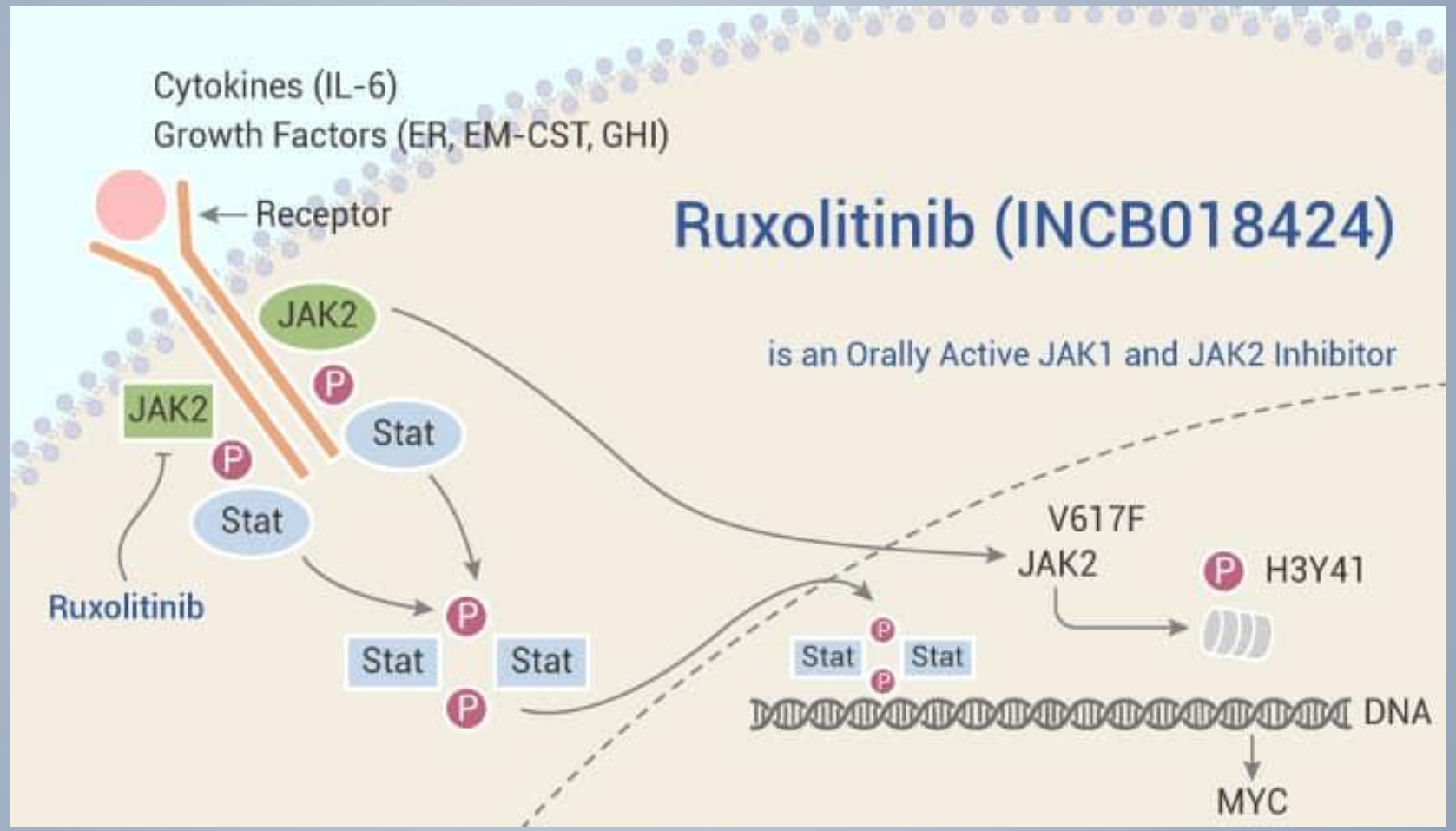
Ruxolitinib (INCB018424)	JAK1/2	FDA approved
Fedratinib (SAR302503)	JAK2/FLT3	
Pacritinib (SB1518)	JAK2/IRAK1	
Momelotinib (CYT387)	JAK1/2 + ACVR1	Potential future candidate
CEP701	JAK1/2	
INCB39110	JAK1	
BMS-911543 (INCB018424)	JAK2	
LY2784544	JAK2/SRC	
NS018*	JAK2	
XL019	JAK2	
AZD1480	JAK2	

Phase 1 → Phase 2 → Phase 3 → Phase 4 → Terminated

*Phase 2b study (NCT04854096) of NS018 in myelofibrosis with platelet count <50 x10^9/L NCT04854096

James T. England &
Vikas Gupta (2022)

Ruxolitinib



PROMYELOCYTIC LEUKEMIA

PML-RARalpha as target of ATRA therapy

t(15;17)(q22;q12)

Focus sulla **Leucemia acuta promielocitica**

PML-RARalfa

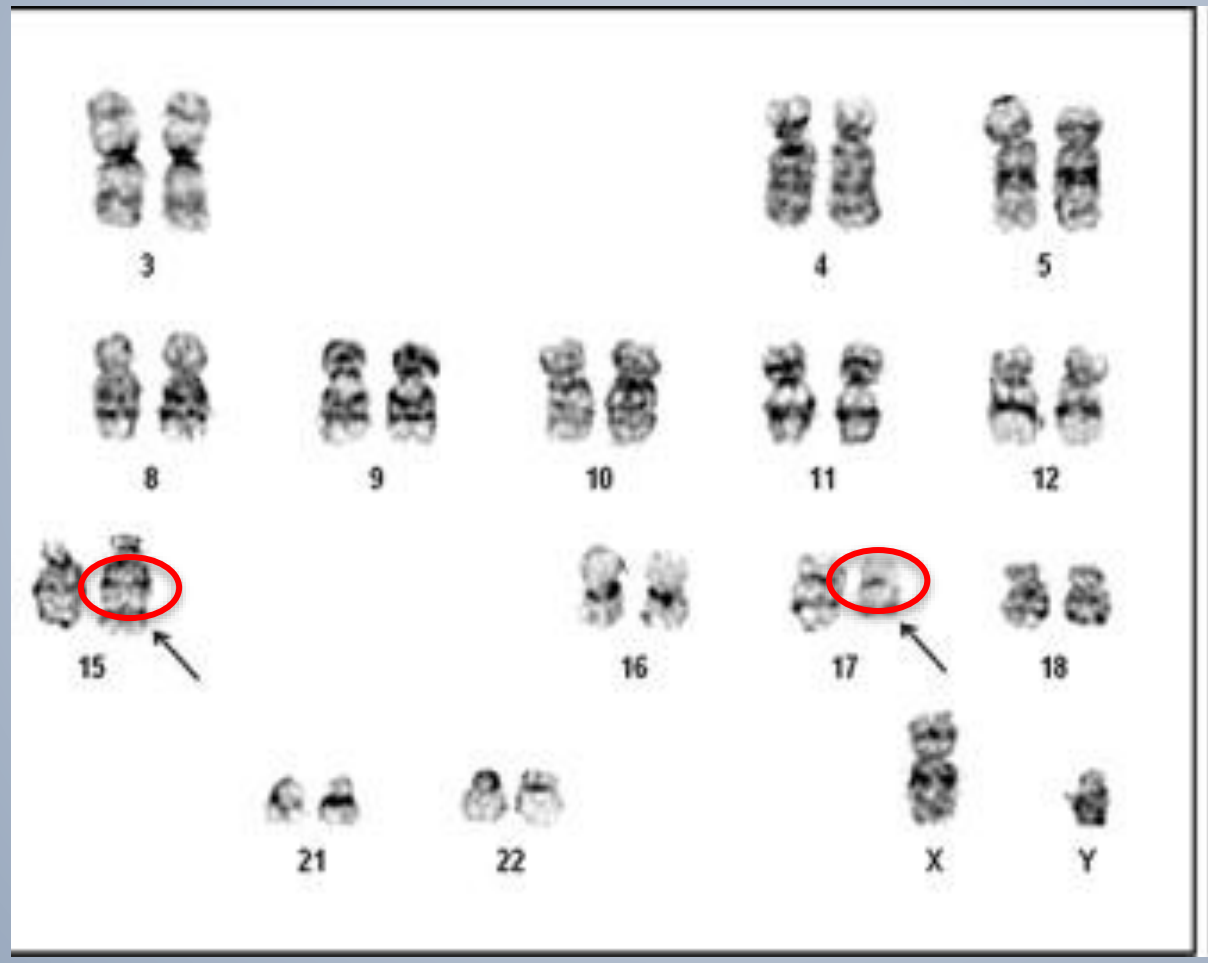
PML: promyelocytic leukemia gene. Ruolo nell'ematopoiesi precoce.

RARalfa: regolatore trascrizionale. Agisce sia come attivatore che come repressore.

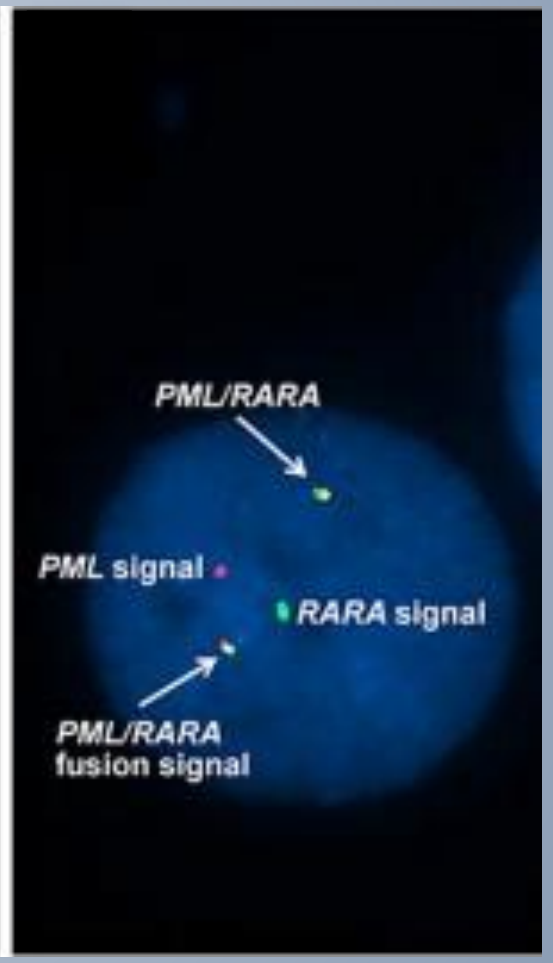
PROGNOSI: negative…ma con la target therapy è diventata positiva

t(15;17)(q22;q12)

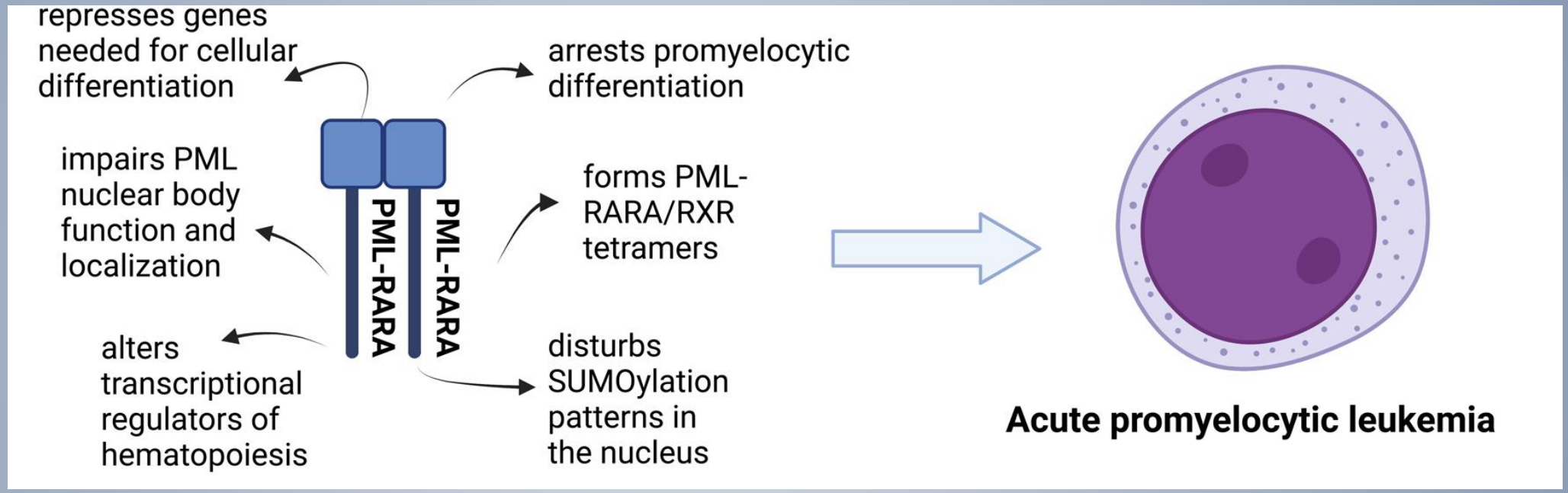
La traslocazione rilevata con il bandeggio classico



La traslocazione rilevata con la FISH

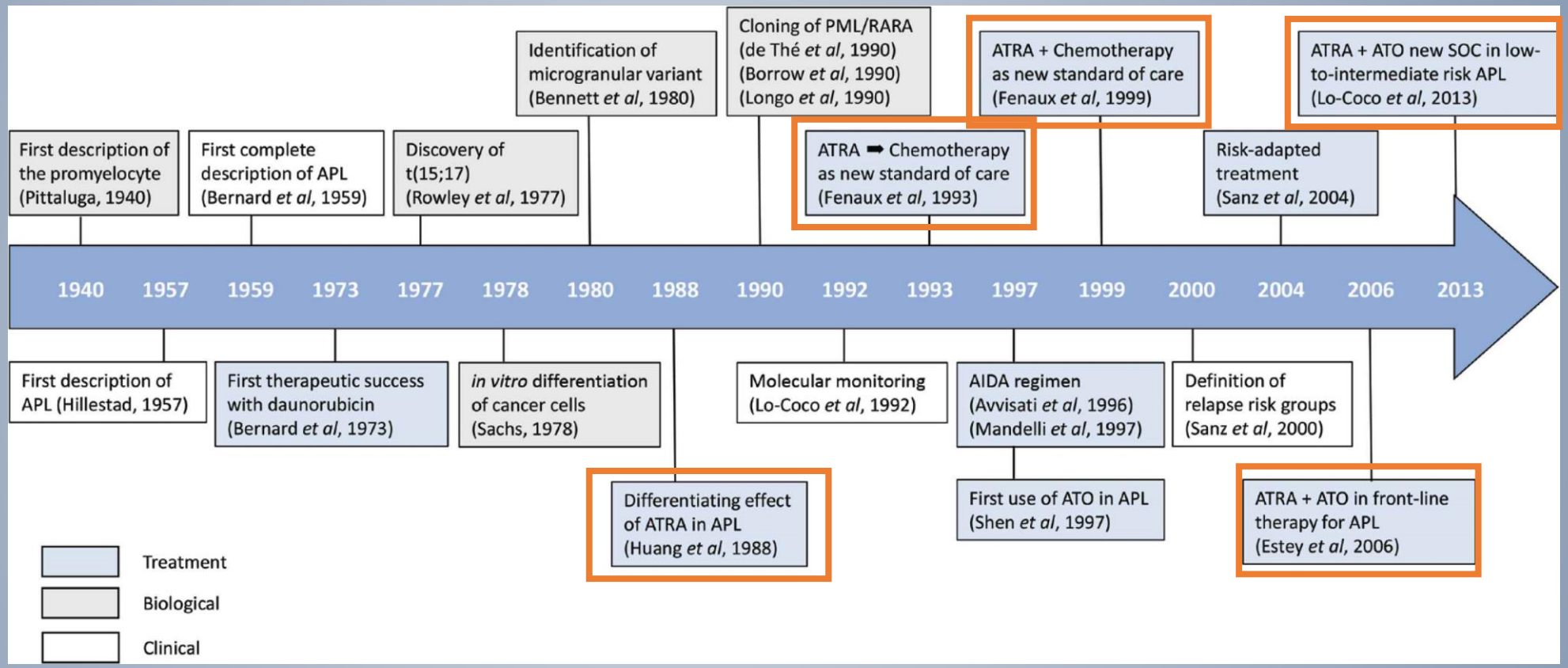


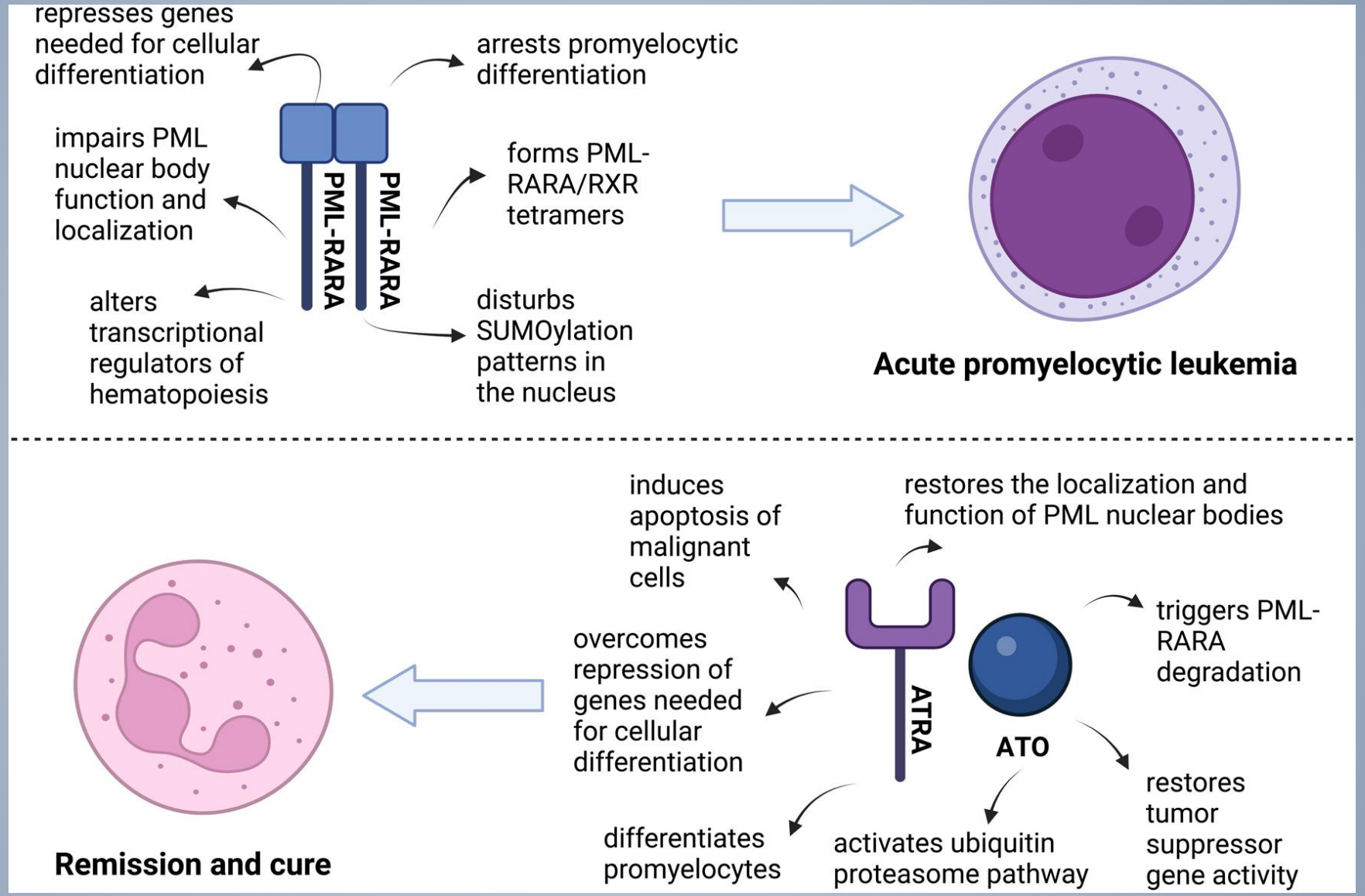
t(15;17)(q22;q12)

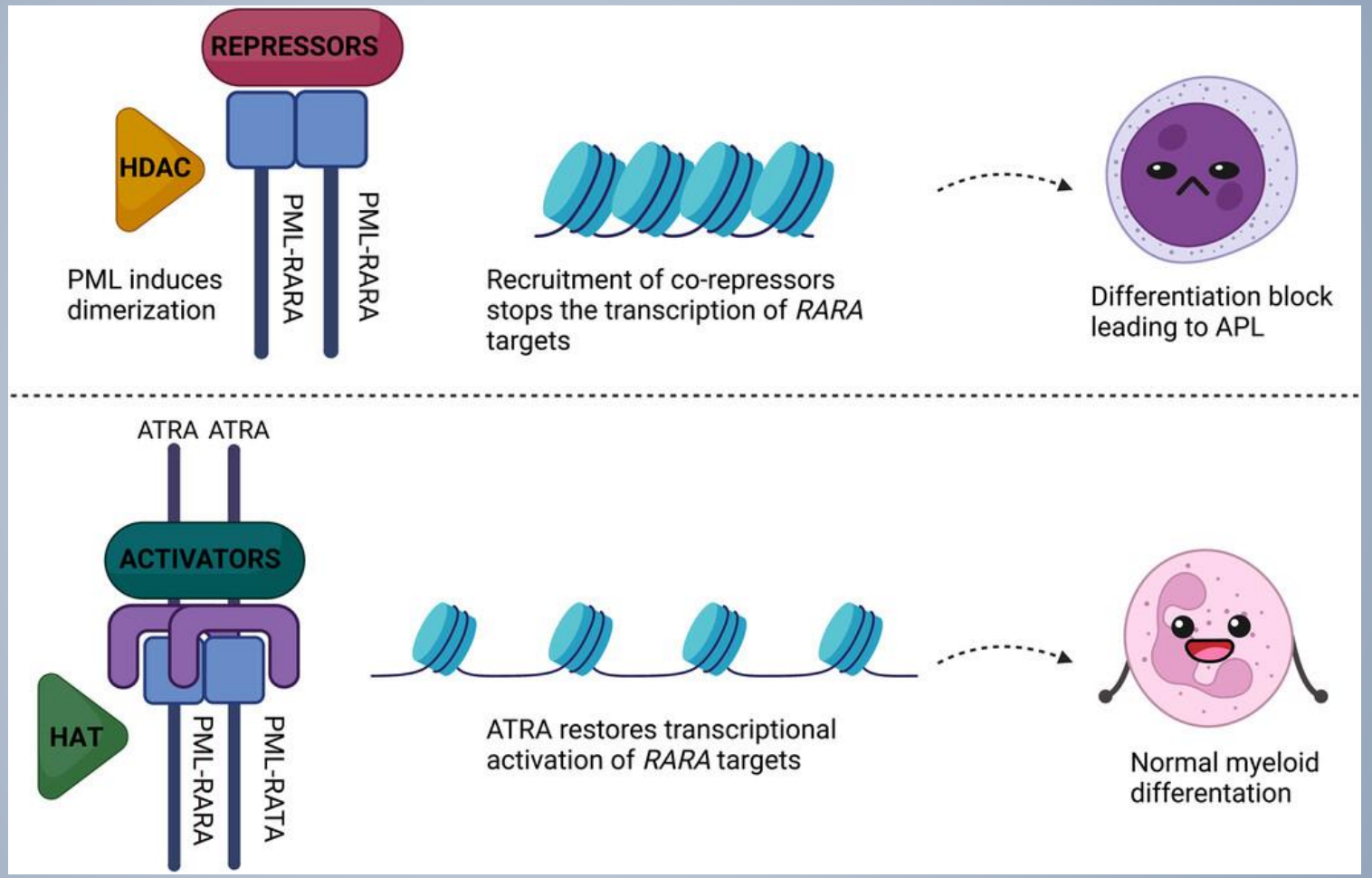


Ipoacetilation of target genes

Evolution of the therapy in PML



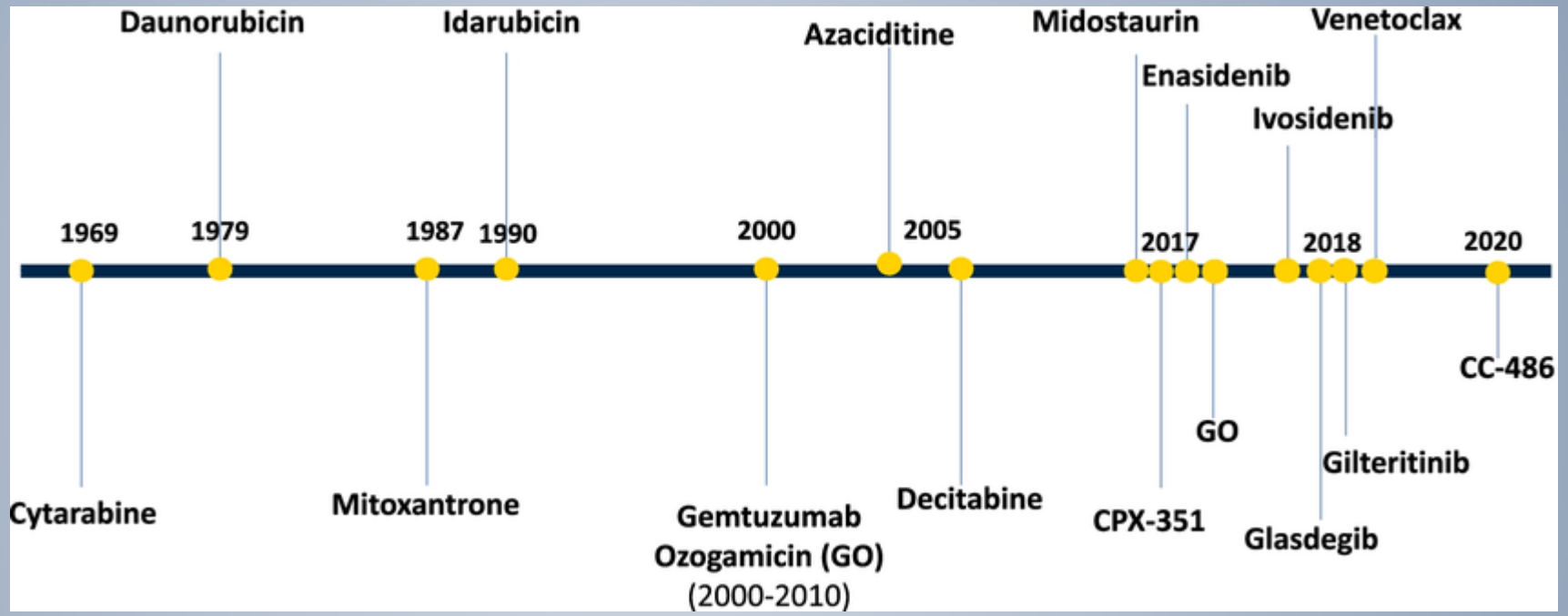

represses genes needed for cellular differentiation
arrests promyelocytic differentiation
impairs PML nuclear body function and localization
forms PML-RARA/RXR tetramers
PML-RARA
PML-RARA
alters transcriptional regulators of hematopoiesis
disturbs SUMOylation patterns in the nucleus
Acute promyelocytic leukemia
induces apoptosis of malignant cells
restores the localization and function of PML nuclear bodies
triggers PML-RARA degradation
overcomes repression of genes needed for cellular differentiation
ATRA
ATO
restores tumor suppressor gene activity
differentiates promyelocytes
activates ubiquitin proteasome pathway
Remission and cure


REPRESSORS
HDAC
PML-RARA
PML-RARA
PML induces dimerization
Recruitment of co-repressors stops the transcription of *RARA* targets
Differentiation block leading to APL
ATRA ATRA
ACTIVATORS
HAT
PML-RARA
PML-RATA
ATRA restores transcriptional activation of *RARA* targets
Normal myeloid differentation

ACUTE MYELOID LEUKEMIA

FLT3-ITD and mutated IDH1-2 as target of target therapy

Evolution of the therapy in AML

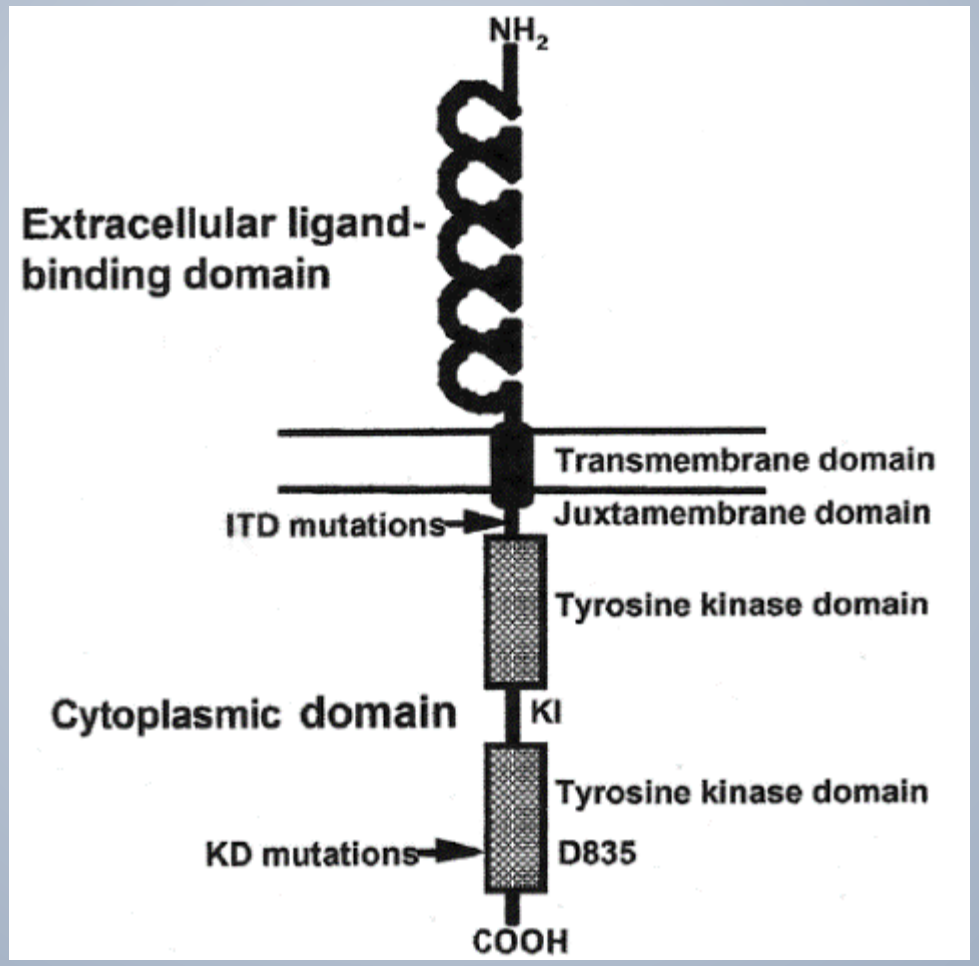


Anti-CD33

60y of aspecific therapy!

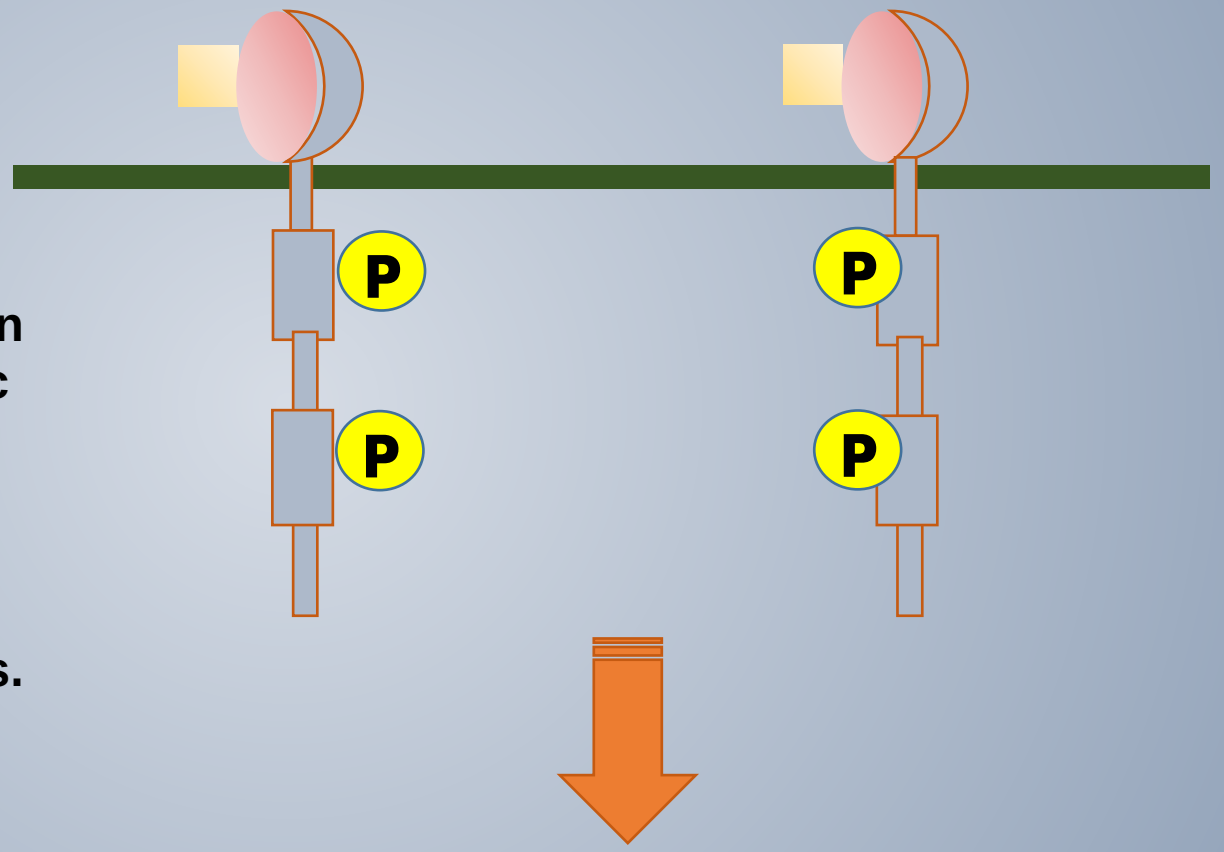
2015 ca
1° target therapy

FLT3


NH2
Extracellular ligand-binding domain
Transmembrane domain
Juxtamembrane domain
ITD mutations
Tyrosine kinase domain
Cytoplasmic domain
KI
Tyrosine kinase domain
KD mutations
D835
COOH

FLT3

Preliminary expressed on immature hematopoietic cells. It is essential for the physiological and normal function and differentiation of hematopoietic stem cells.



Regolazione della differenziazione, sopravvivenza, proliferazione e apoptosi

FLT3

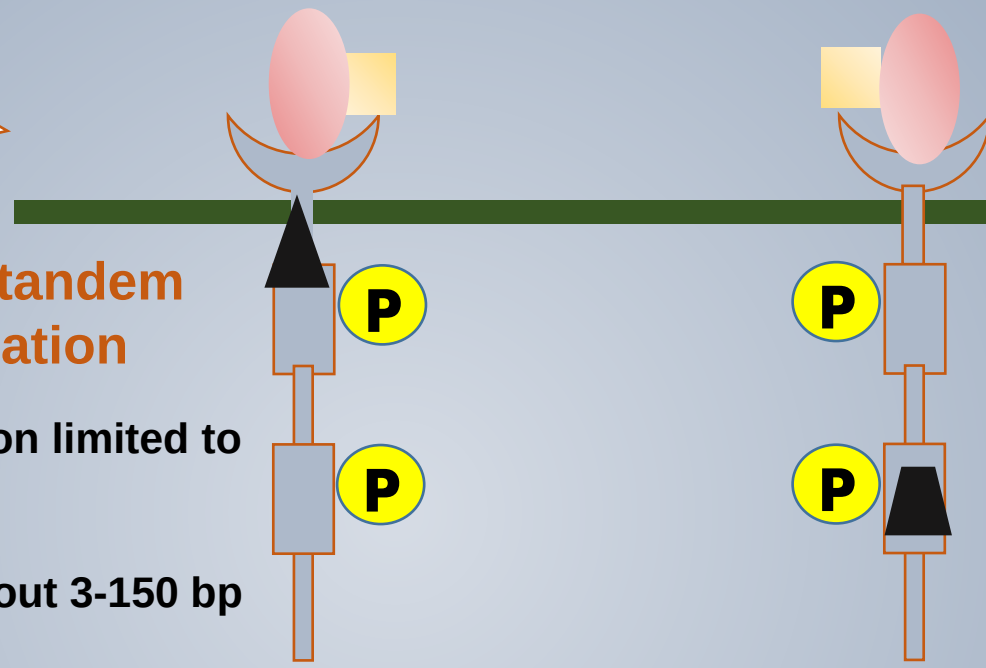
15-35%

Internal tandem duplication

Structural mutation limited to JM

Duplication of about 3-150 bp

Loss of auto-inhibition to move from inactive to active form based on ligand recognition.



~7%

Activation Loop mutation

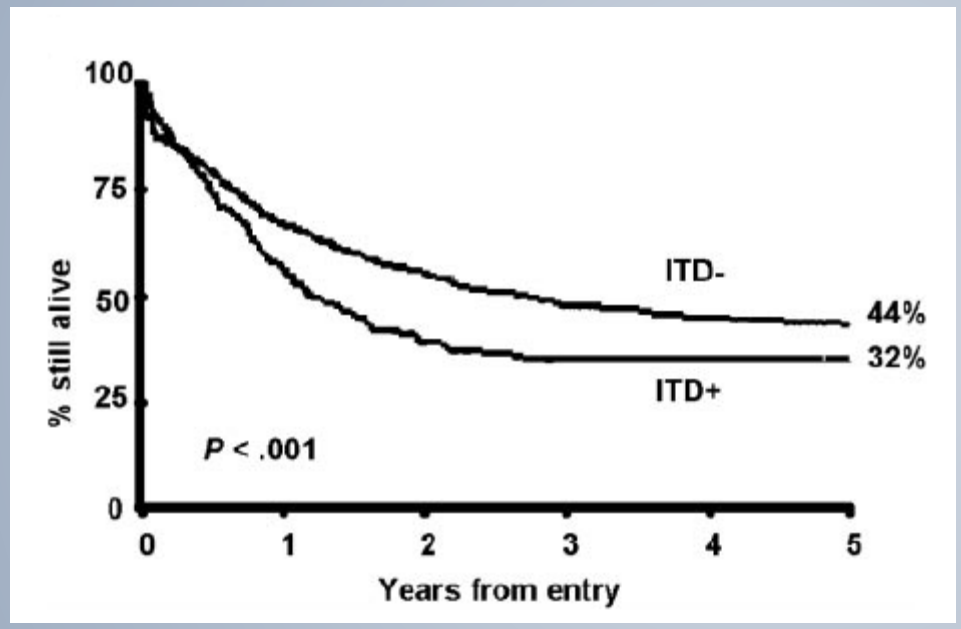
Point mutation of the TK domain. It induces the modification of the codon 835 (Asp835Tyr, but also in Val, His, Glu, Asn)

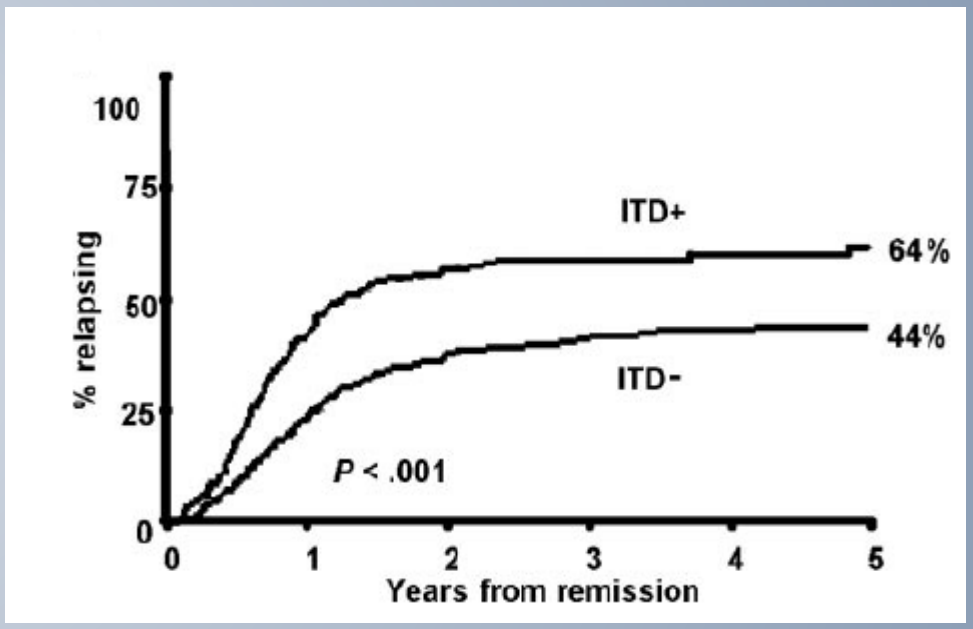
Auto-phosphorilation that determins the auto-activation

Prognosis very severe

Cellular proliferation

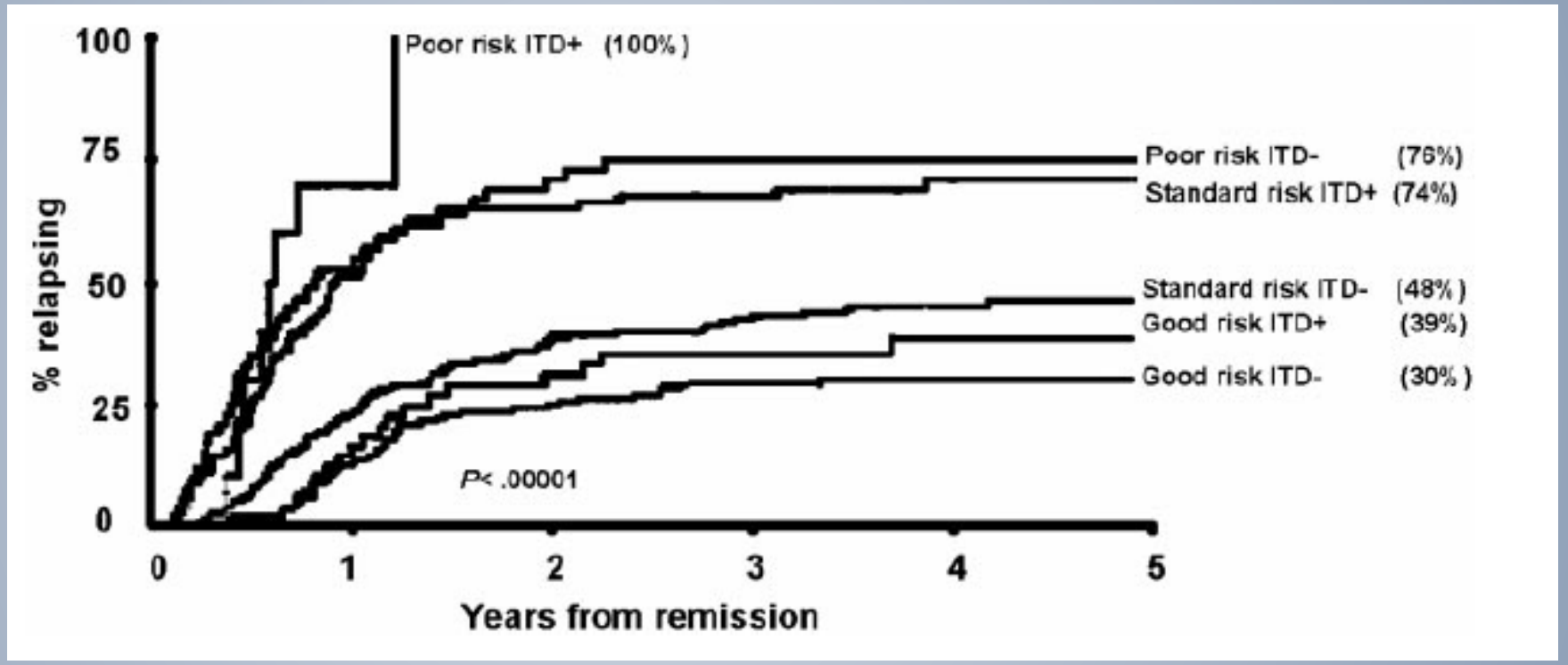
FLT3





Panajotis D et al. Blood 2001; 98: 1752

FLT3



Panajotis D et al. Blood 2001; 98: 1752

First and next-generation FLT3 inhibitors

	Key pathways targeted (in addition to FLT3)	Developmental phase	Main toxicities
First-generation FLT3 inhibitors			
Sunitinib	VEGFR2, PDGFRβ, KIT, RET	Phase 2	Decreased appetite, headache, GI symptoms
Sorafenib	RAF, VEGFR1/2/3, PDGFRβ, KIT, RET	Phase 3	Skin rash, fatigue, diarrhea
Midostaurin	PKC, SYK, FLK-1, AKT, PKA, KIT, FGR, SRC, PDGFRα/β, VEGFR1/2	Approved for the treatment of newly diagnosed *FLT3*-mutated AML in combination with chemotherapy	Fever, flu-like symptoms, mouth sores, unusual bleeding or bruising
Lestaurtinib	JAK2/3, TrkA/B/C	Phase 2	Infections, sepsis, myocardial infarction
Ponatinib	LYN, ABL, PDGFRα, VEGFR2, FGFR1, SRC, KIT, TEK, RET	Phase 2	Pancreatitis
Tandutinib	KIT, PDGFRβ	Withdrawn	Muscle weakness
KW-2449	ABL, aurora kinase	Withdrawn	NA
Next-generation FLT3 inhibitors			
Crenolanib	PDGFRβ	Phase 3	Nausea, vomiting, transaminitis, fluid retention
Quizartinib	KIT, PDGFR	Phase 3	QTcF prolongation (especially at higher doses)
Gilteritinib	LTK, ALK, AXL	Phase 3	Diarrhea, fatigue, high liver function tests

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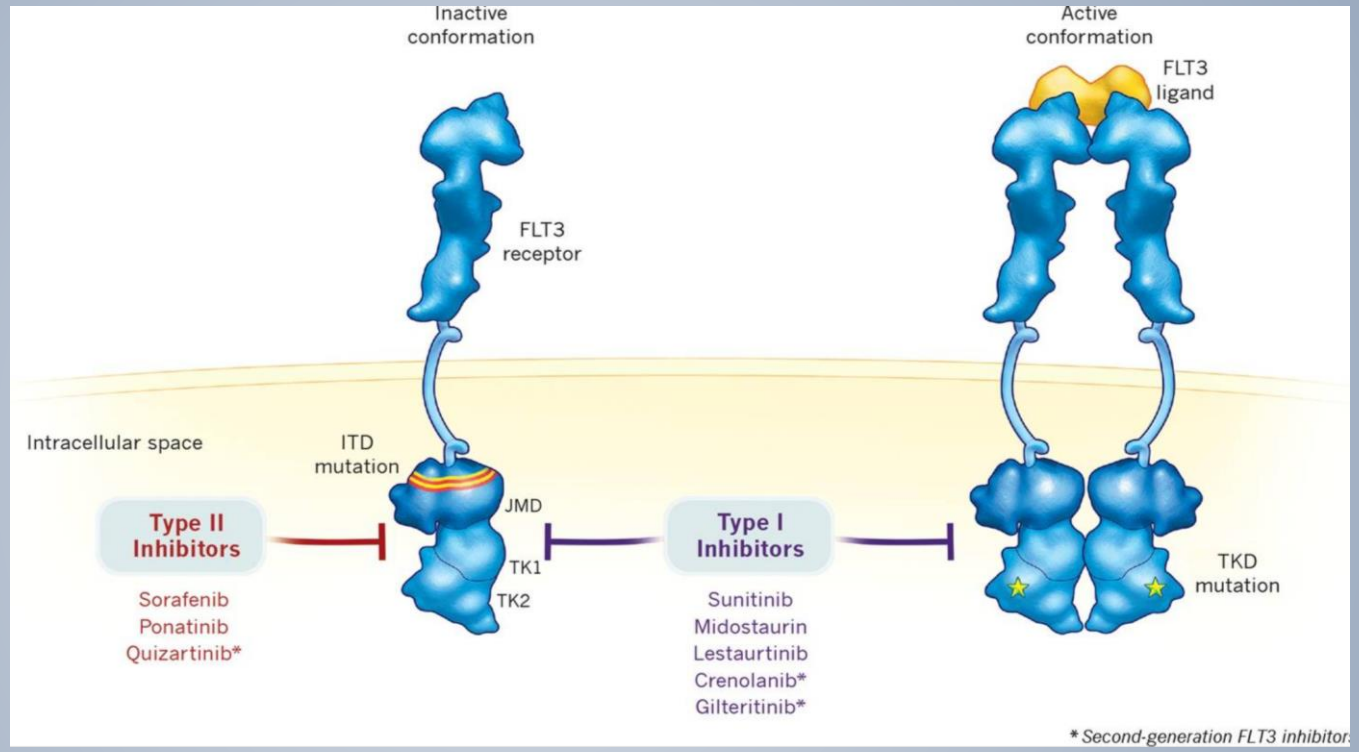
FGFR fibroblast growth factor receptor, *FLT3* FMS-like tyrosine kinase 3, *GI* gastrointestinal, *JAK* Janus kinase, *NA* not applicable, *PDGFR* platelet-derived growth factor receptor, *PK* protein kinase, *VEGFR* vascular endothelial growth factor receptor

Midostaurin is used in first line and the most used in general

Gilteritinib (Xospata) is approved for relapsed/refractory patients

Daver N et al, Leukemia 2019

Different mechanisms of action

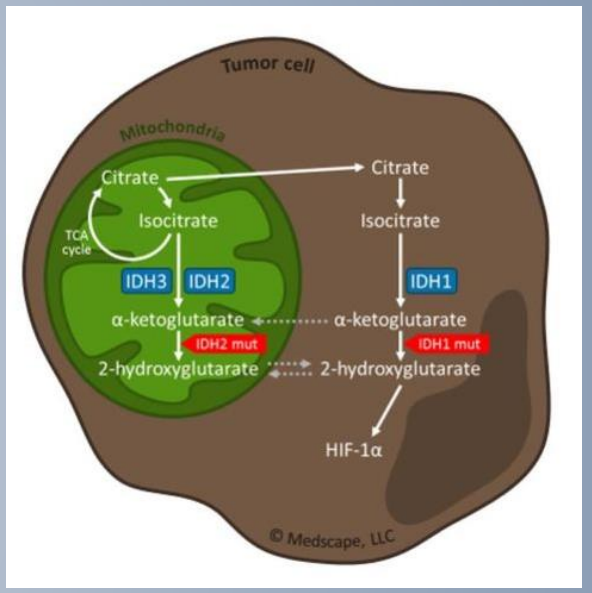


Type I FLT3 inhibitors bind the FLT3 receptor in the active conformation, either near the activation loop or the ATP-binding pocket and are active against ITD and TKD mutations. Type II FLT3 inhibitors bind the FLT3 receptor in the inactive conformation in a region adjacent to the ATP-binding domain. As a result of this binding affinity, type II FLT3 inhibitors prevent activity of ITD mutations but do not target TKD mutations

Daver N et al, Leukemia 2019

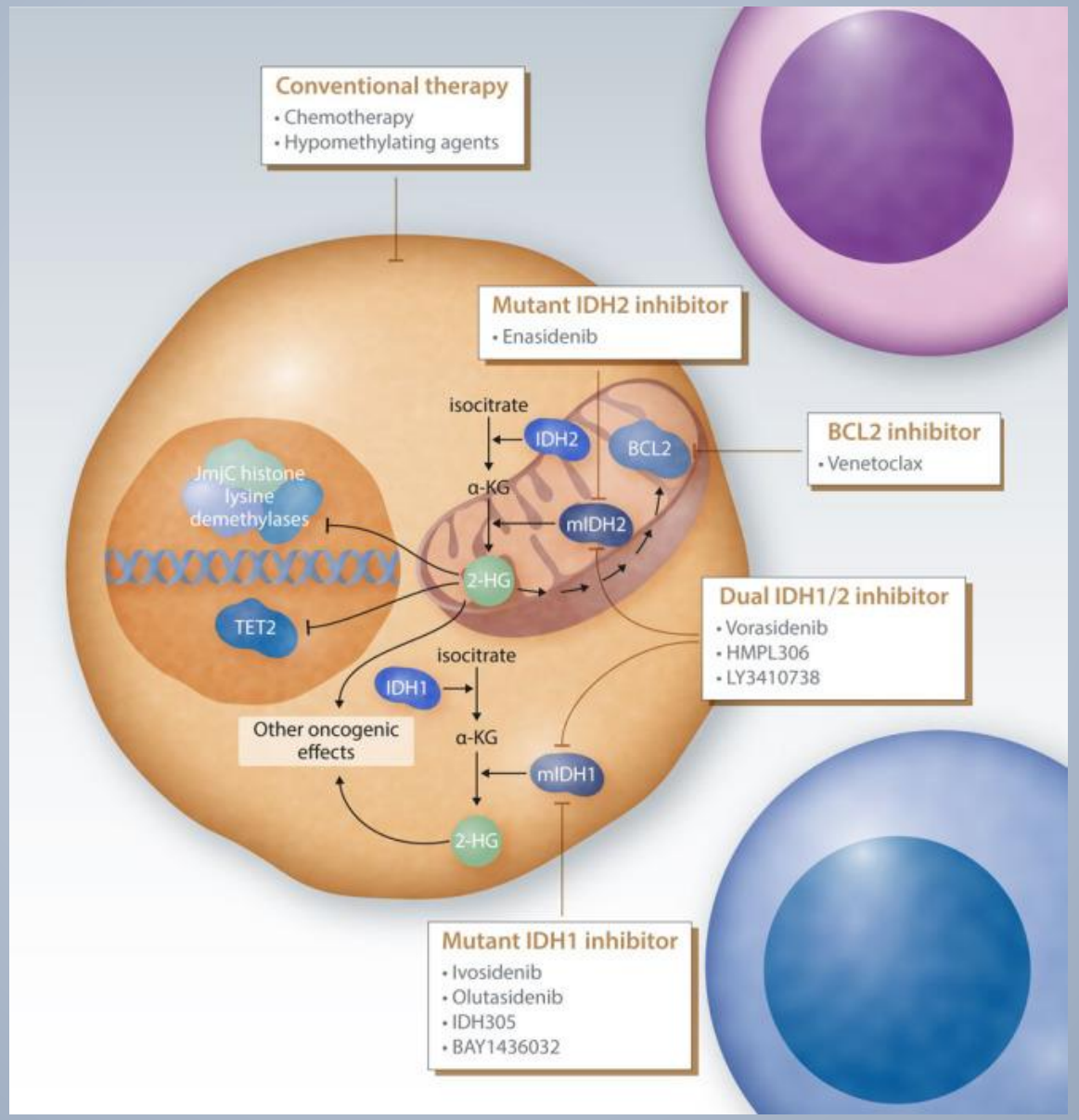
IDH1-2

- Isocitrate dehydrogenase (IDH) is a critical enzyme of the citric acid cycle
- IDH mutations occours in a spectrum of solid and hematologic tumors
- IDH1 mutations in AML were significantly associated with normal karyotype and NPM1 mutations
- IDH1mut: 6-10% AML, 3%MDS
- IDH2mut: 8-13% AML, 3-6% MDS
- IDH1/2 mutations confer a gain of function: production of 2-hydroxyglutarate (2-HG)
- 2-HG drives multiple oncogenic processes: increased histone and DNA methylation, and impaired cellular differentiation
- Clinical proof of concept established in hematologic cancers: AG-221 (IDH2mut), and AG-120 (IDH1mut)

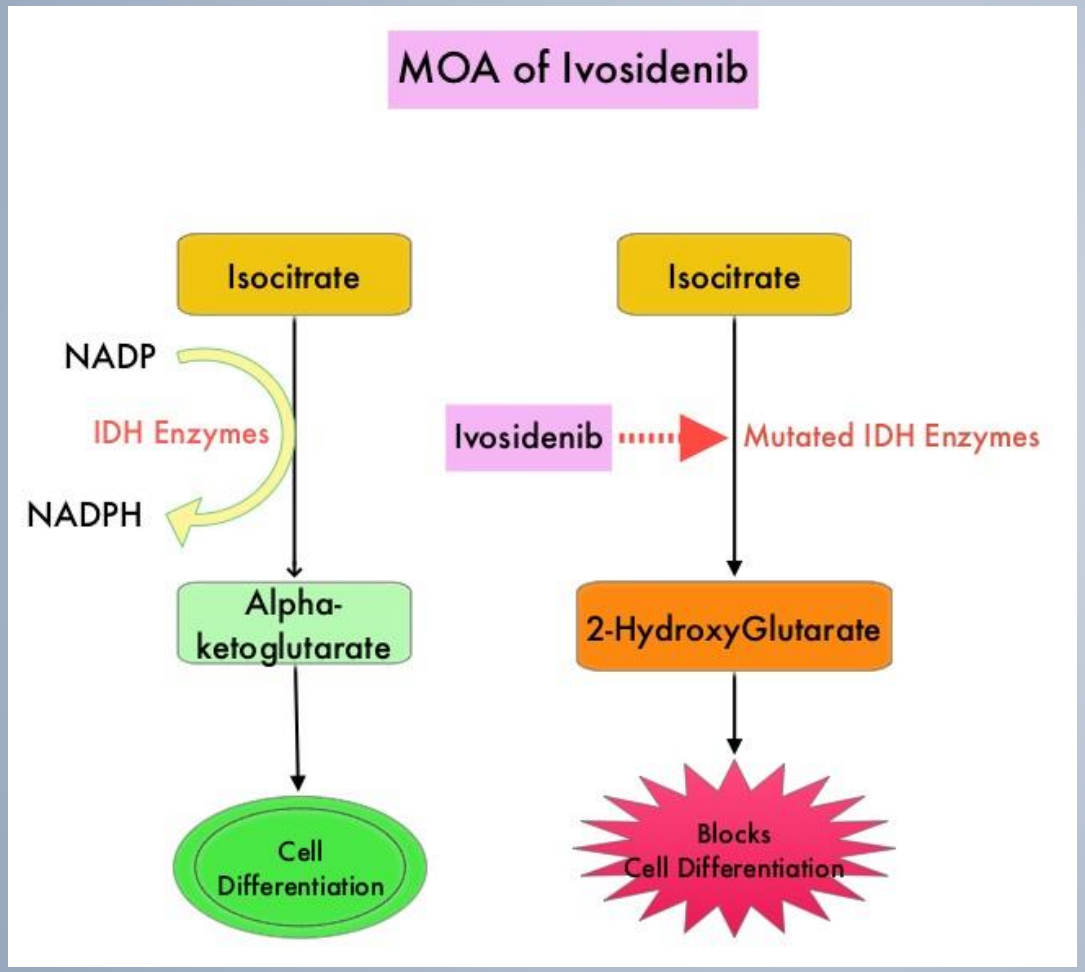


IDH1 in the cytoplasma
IDH2 in the mitochondria

IDH1-2

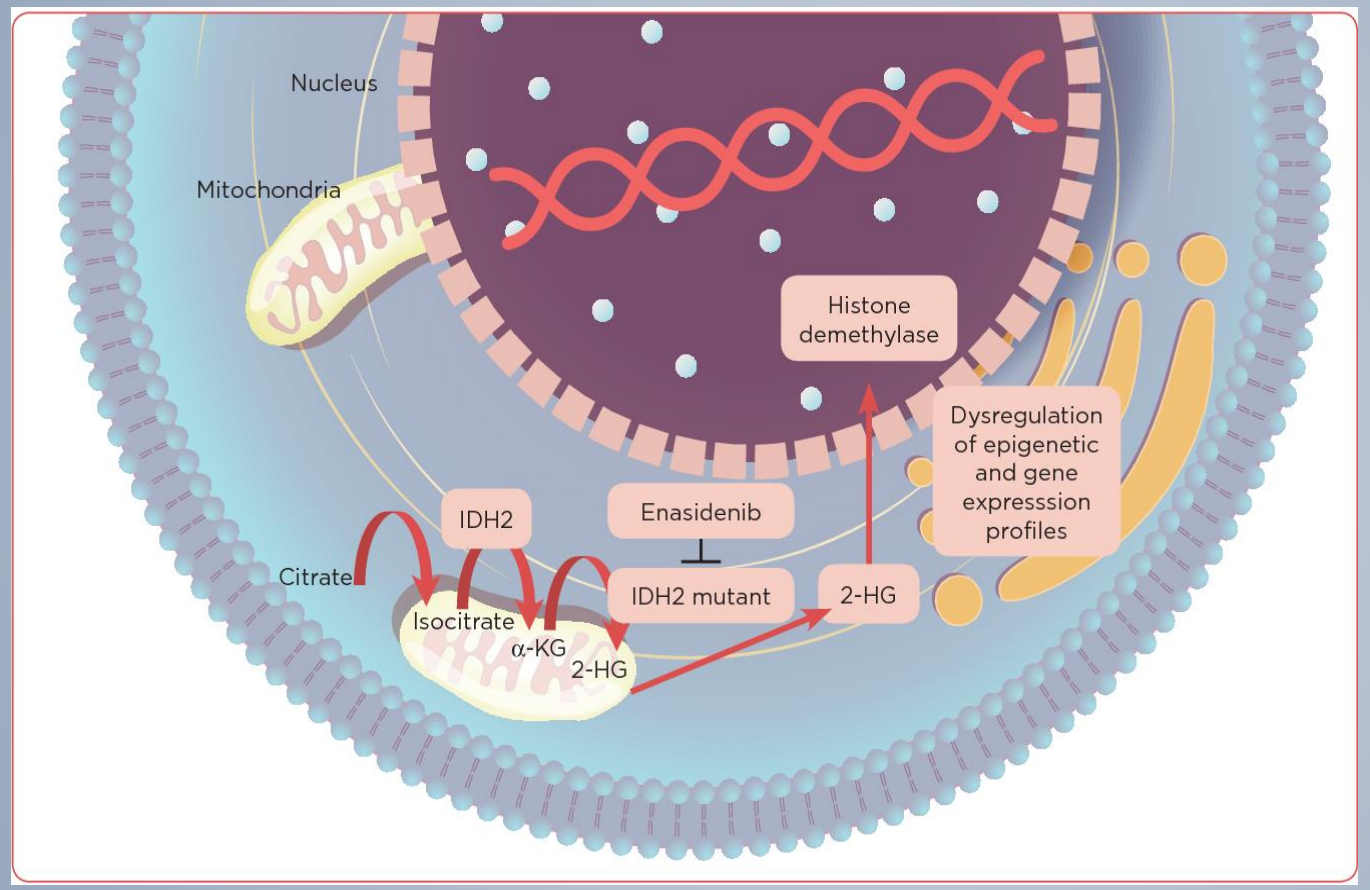

Conventional therapy
• Chemotherapy
• Hypomethylating agents
Mutant IDH2 inhibitor
• Enasidenib
isocitrate
IDH2
BCL2
BCL2 inhibitor
• Venetoclax
α-KG
mIDH2
JmjC histone lysine demethylases
2-HG
TET2
Dual IDH1/2 inhibitor
• Vorasidenib
• HMPL306
• LY3410738
isocitrate
IDH1
Other oncogenic effects
α-KG
mIDH1
2-HG
Mutant IDH1 inhibitor
• Ivosidenib
• Olutasidenib
• IDH305
• BAY1436032

Ivosidenib (AG120): IDH1 Inhibitor



- Oral IDH1 Mutant Enzyme Inhibitor for AML
- 250mg/bidie standard dose
- Successfully administered in combination with azacitidine obtainining improved EFS, OS, and a good tolleration

Enasidenib (AG221): IDH2 Inhibitor



- Oral IDH2 Mutant Enzymes Inhibitor for AML
- 100mg/die standard dose
- High efficacy (CR and ORR) and well tollerated also in elderly

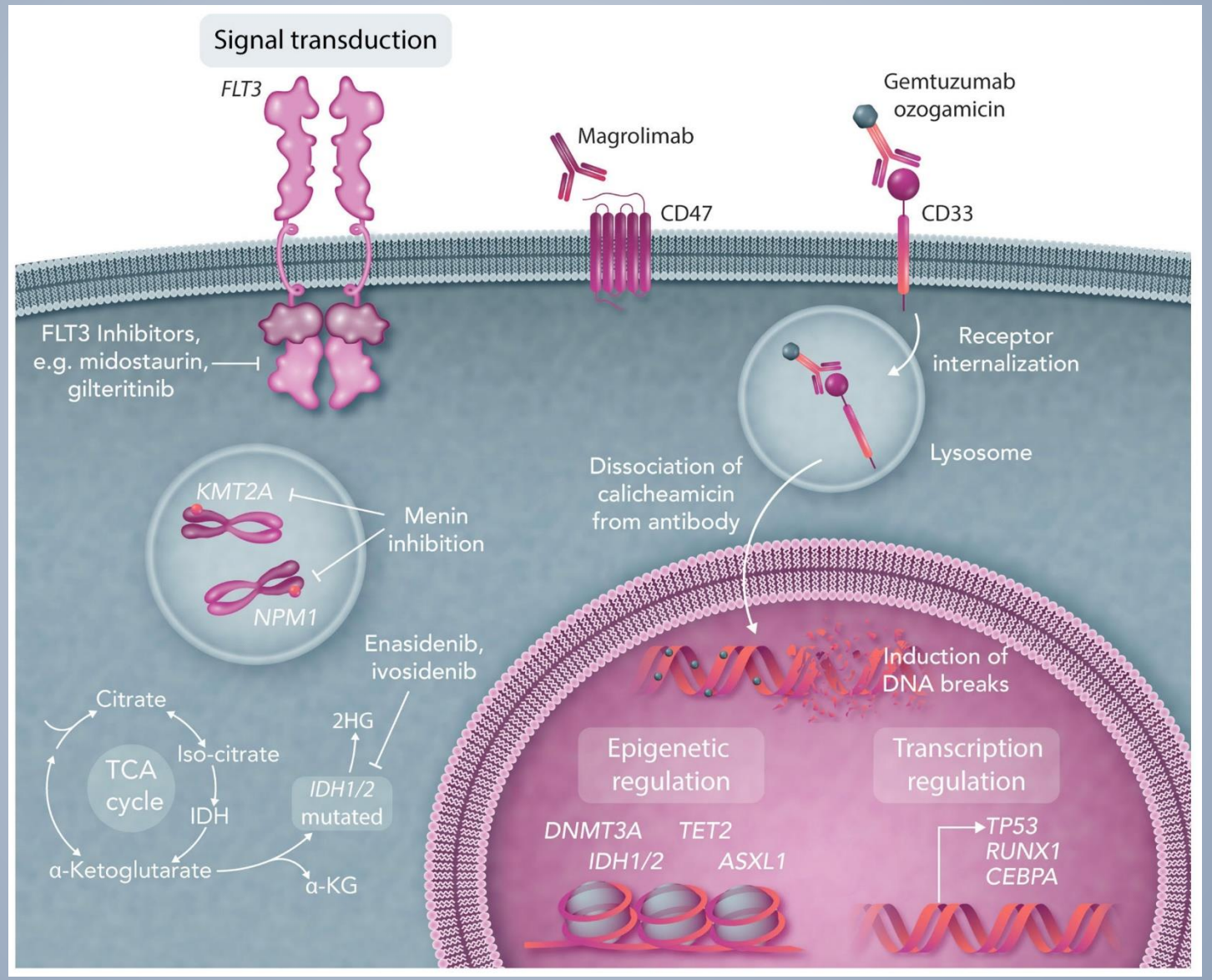
Enasidenib: IDH2 Inhibitor

Phase Ib/II Study of Enasidenib plus Venetoclax in *IDH2*-Mutated R/R MDS or AML

Conclusion

- Enasidenib plus Venetoclax is well tolerated in patients with *IDH2*-mut R/R AML or MDS
  - Adverse events primarily grade 1-2
  - **No differentiation syndrome** or tumor lysis syndrome
  - **No significant myelosuppression**; infection rate as expected for R/R MDS/AML
- Enasidenib plus Venetoclax shows promising efficacy in *IDH2*-mutated R/R AML or MDS
  - In patients in *IDH2*-mutated R/R AML: **ORR of 70%**
  - **ORR** was higher in patients with ***IDH2* R172** mutations: **ORR 83% vs 55%** (R140)
  - **Median OS 9.4 months** [95% CI, 8.2 - NR] and **18-month OS 42%** [95% CI, 27 - 66]
  - **DOR 16.6 months** [95% CI, 5.0 - NR]
- Combination therapy using combination of IDH2 and BCL2 inhibitors in *IDH2*-mutated MDS/AML warrants further study

Recap


Signal transduction
FLT3
Magrolimab
CD47
Gemtuzumab ozogamicin
CD33
FLT3 Inhibitors, e.g. midostaurin, gilteritinib
Receptor internalization
Lysosome
Dissociation of calicheamicin from antibody
KMT2A
NPM1
Menin inhibition
Enasidenib, ivosidenib
Citrate
Iso-citrate
TCA cycle
IDH
α-Ketoglutarate
2HG
IDH1/2 mutated
α-KG
Induction of DNA breaks
Epigenetic regulation
Transcription regulation
DNMT3A
TET2
IDH1/2
ASXL1
TP53
RUNX1
CEBPA