CHRONIC MYELOID LEUKEMIA

LESSENREEKS KLINISCHE BIOLOGIE

15-02-2022

N. BOECKX, MD, PHD

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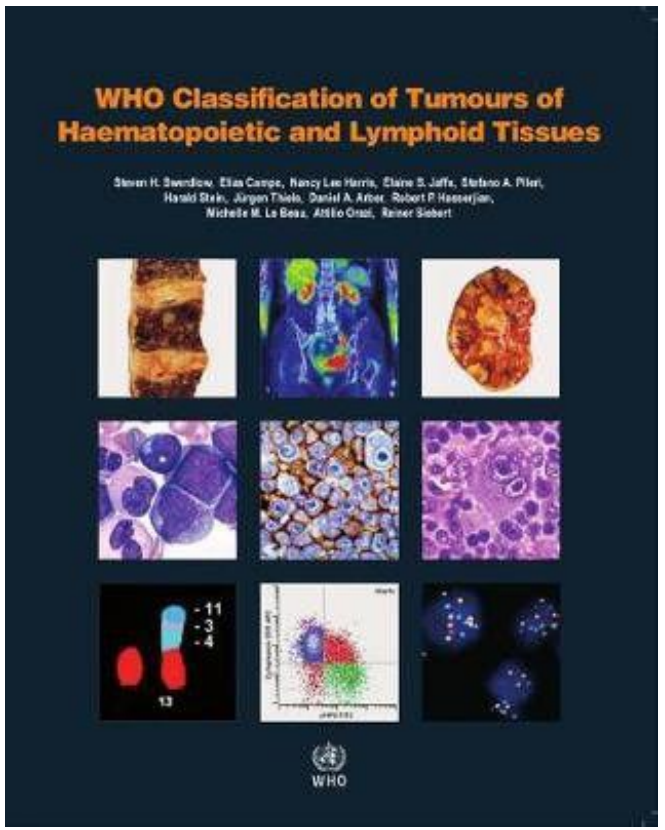

WHO classification 2018

Myeloproliferative neoplasm

- Chronic myeloid leukemia, *BCR::ABL1* positive
- Chronic neutrophililc leukemia
- Polycythemia vera
- Primary myelofibrosis
  - Prefibrotic/early primary myelofibrosis
  - Overt primary myelofibrosis
- Essential thrombocythaemia
- Chronic eosinophilic leukemia, not otherwise specified
- Myeloproliferative neoplasm, unclassifiable

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WHO 2018

- Granulocytes are the major proliferative component
- Arises in a hematopoietic stem cell
- Characterized by the t(9;22)(q34.1;q11.2)
  - formation of Ph chromosome, containing the *BCR::ABL1* fusion gene
- *BCR::ABL1* is found in all myeloid lineages, in some lymphoid cells
- Natural history is biphasic or triphasic
  - Initial indolent chronic phase (CP)
  - Followed by:
    - accelerated phase (AP)
    - blastic phase (BP)

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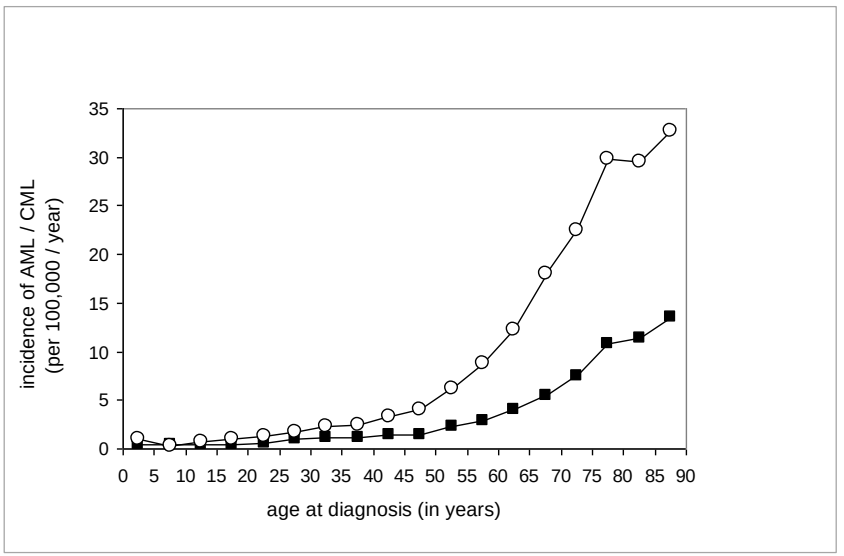
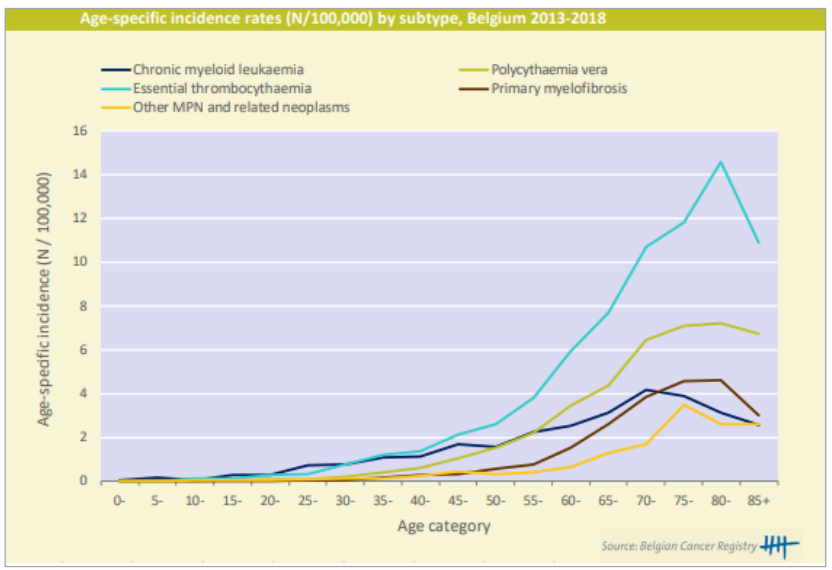
EPIDEMIOLOGY

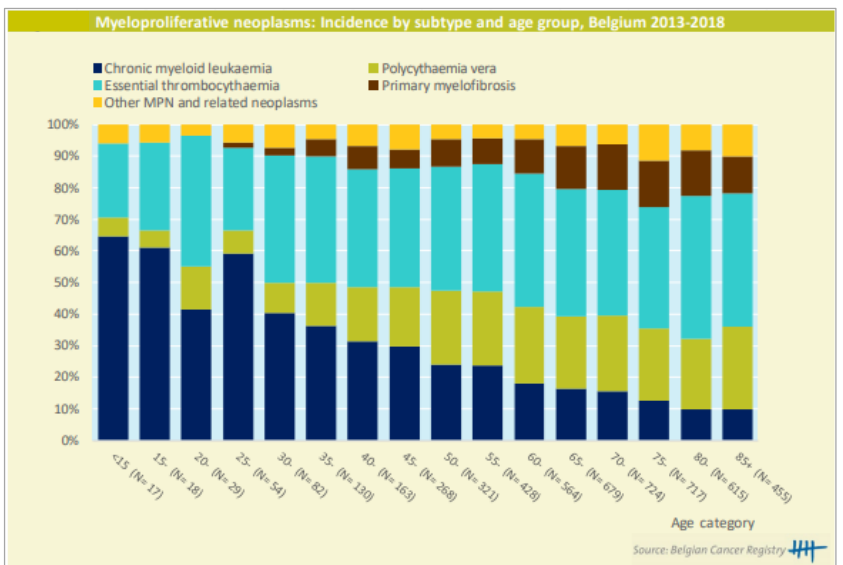
- annual incidence of 1-2 cases/100.000 population
- slight male predominance (M/F: 1.6/1)
- median age 57 years in Western countries
  - patients >70 years make up >20%
  - children/adolescents <5%
- annual incidence increases with age
  - < 0,1 cases / 100.000 children
  - ≥ 2,5 cases / 100.000 elderly individuals



Age-specific incidence of AML and CML in the Netherlands (1994-1998) [4]

EPIDEMIOLOGY





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Belgian Cancer Registry (2013-2018)

ETIOLOGY

- Predisposing factors are largely unknown
- Acute radiation exposure: increased risk (reported increased incidence of CML among atomic bomb survivors)
- No known familial associations
- Not a frequent secondary leukemia

CLINICAL FEATURES

- most cases diagnosed in CP, onset usually insidious
- +/-50% asymptomatic, discovered by chance
- if symptomatic: common findings: fatigue, malaise, weight loss, night sweats, anemia, palpable splenomegaly (50%)
- atypical presentations: marked thrombocytosis without leukocytosis
- <5% diagnosed in AP or BP without a recognized CP

NATURAL HISTORY OF CML

Accumulation of immature myeloid cells
New cytogenetic findings

	Chronic phase	Accelerated Phase	Blast phase
Duration	if untreated, 3-5 yrs	Varies (6-9 months)	Median survival of several months (3-6 months)
Symptoms	Asymptomatic, OR Fatigue Abdominal pain or discomfort Weight loss Night sweats	Progressive splenomegaly Myelofibrosis	Bleeding complications Infection complications Complications due to severe anemia

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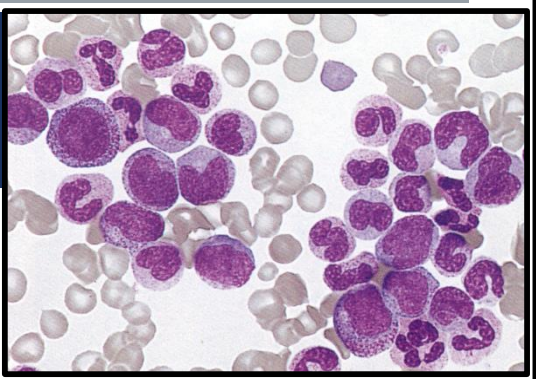
MICROSCOPY CP



Peripheral blood

- Leucocytosis (12-1000 x10e9/L): neutrophils and immature myeloid cells
  - Children often higher WBC counts (median 250x10e9/L) then adults (median 80x10e9/L)
- No significant granulocytic dysplasia
- Blasts <2%
- Absolute basophilia / eosinophilia are common
- Absolute monocytosis, but relative <3% monocytes (except rare cases with the p190 BCR::ABL1 isoform which mimics CMML)
- Platelets: normal to increased (>1000x10e9/L)

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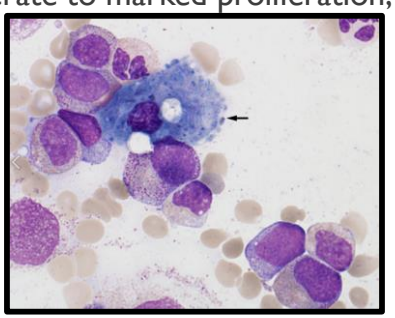
MICROSCOPY CP

Bone marrow

- Hypercellular : marked granulocytic proliferation
- No significant dysplasia
- Blasts usually <5%
- Erythroid precursors is decreased
- Megakaryocytes: normal to slightly decreased, or moderate to marked proliferation, smaller, hyposegmented
- Eosinophils and basophils are increased
- Pseudo-Gaucher cells are common



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DEFINING CRITERIA FOR AP AND BP OF CML

	Accelerated phase		Blast phase	
	WHO	**ELN**	**WHO**	**ELN**
Spleen	Persisting or increasing splenomegaly unresponsive to therapy	–	–	–
WBC count	Persisting or increasing WBC count ($>10 \times 10^9$/L) unresponsive to therapy	–	–	–
Blast cells[a]	10%–19%	15%–29%	≥ 20%	≥ 30%
Basophils[a]	> 20%	> 20%	–	–
Platelet count	$>1000 \times 10^9$/L uncontrolled by therapy	–	–	–
	$<100 \times 10^9$/L unrelated to therapy	Yes	–	–
CCA/Ph+	Any new clonal aberration during therapy Additional clonal chromosomal abnormalities in Ph cells at diagnosis that include 'major route' abnormalities (second Ph, trisomy 8, isochromosome 17q, trisomy 19), complex karyotype or abnormalities of 3q26.2	Present	–	–
Extramedullary involvement[b]	–	–	Present	Present
'Provisional' response-to-TKI criteria	Haematological resistance to the first TKI (or failure to achieve a complete haematological response[c] to the first TKI) or Any haematological, cytogenetic or molecular indications of resistance to 2 sequential TKIs or Occurrence of 2 or more mutations in BCR–ABL1 during TKI therapy			

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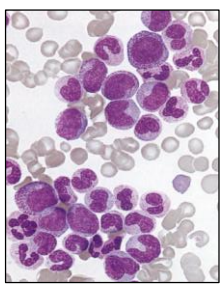
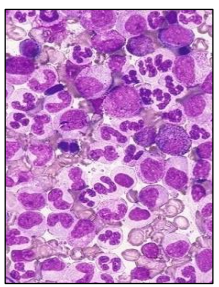
Hochhaus et al. Clin Pract Guid Ann Onc. (2017), Suppl 4

DIAGNOSIS OF CML

Haematologic



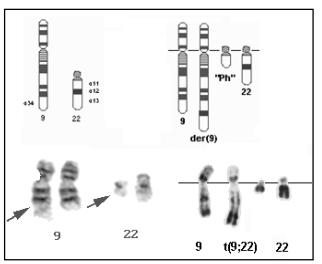
Peripheral blood (with myeloid cells)



Bone marrow (with myeloid hyperplasia)

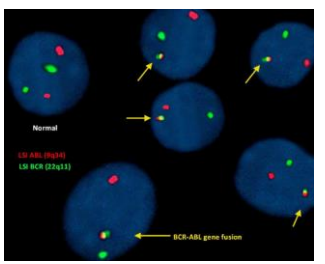
Cytogenetic

Karyotype



Chromosomal translocation t(9;22)(q34.1;q11.2)
Ph chromosome

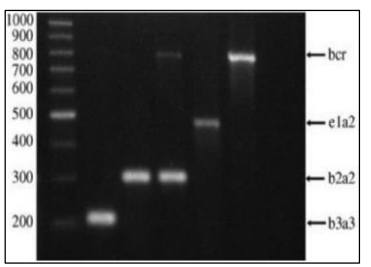
FISH



BCR::ABL1 fusion gene

Molecular

PCR



BCR::ABL1 fusion gene

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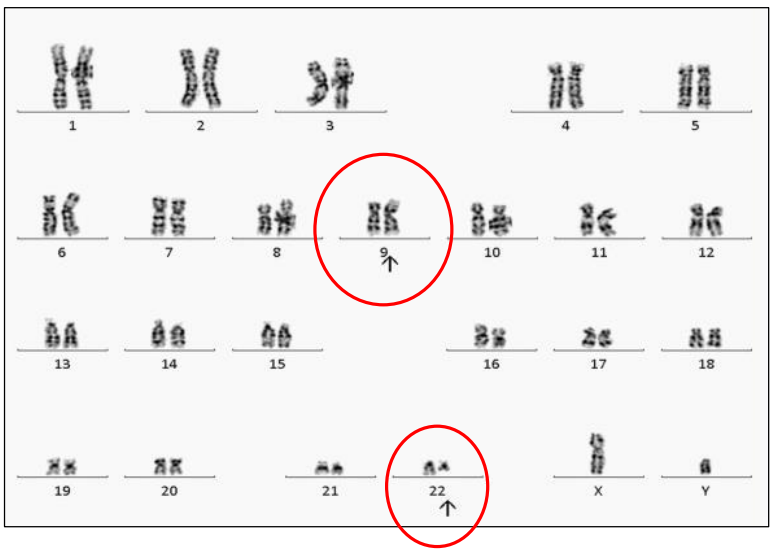
GENETIC PROFILE

- At diagnosis: 90-95% have chromosomal translocation t(9;22)(q34.1;q11.2), Ph chromosome
- In AP or BP additional cytogenetic abnormalities (in >80%) may be seen:
  - trisomy 8
  - trisomy 19
  - duplication of the Ph chromosome
  - isochromosome 17q (leading to the loss of the P53 gene on 17p)



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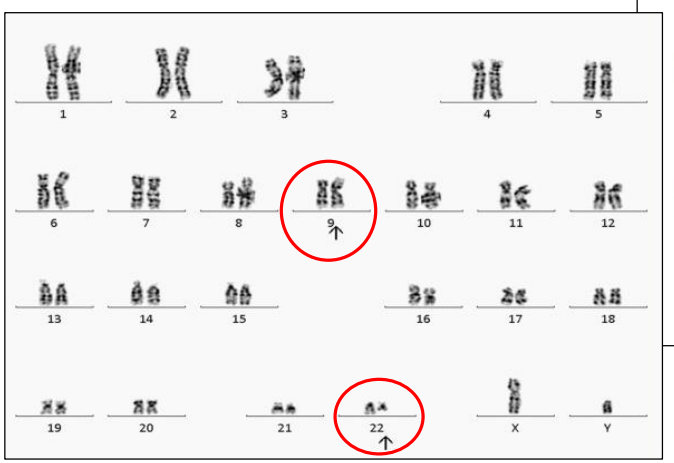

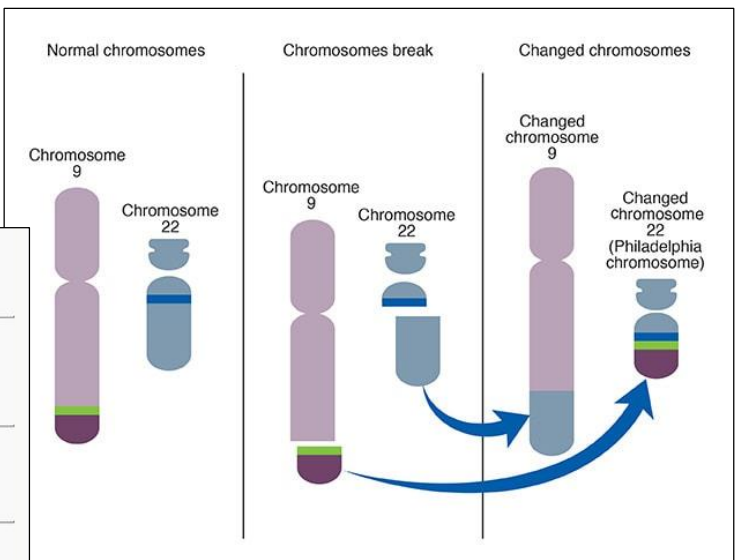

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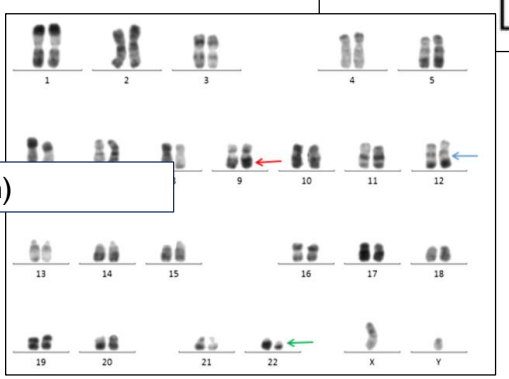
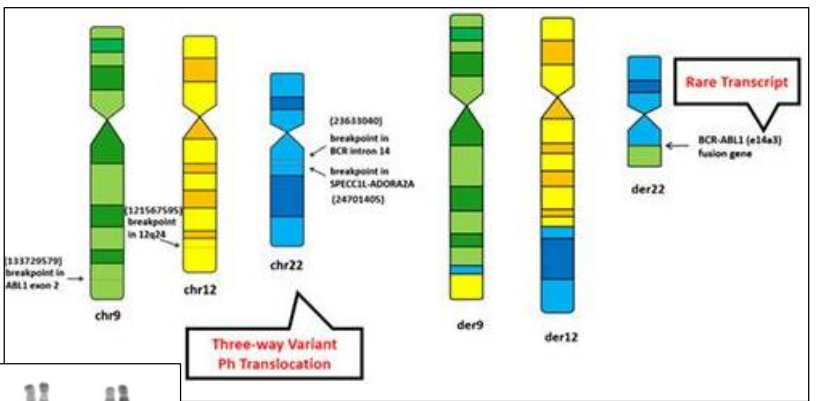
GENETIC PROFILE

- At diagnosis: 90-95% have chromosomal translocation t(9;22)(q34.1;q11.2), Ph chromosome
- Remaining cases:
  - variant translocations (involving a 3rd or 4th chromosome)

FISH and/or PCR (*BCR::ABL1* fusion)





t(9;22;12) variant Philadelphia (Ph) chromosome

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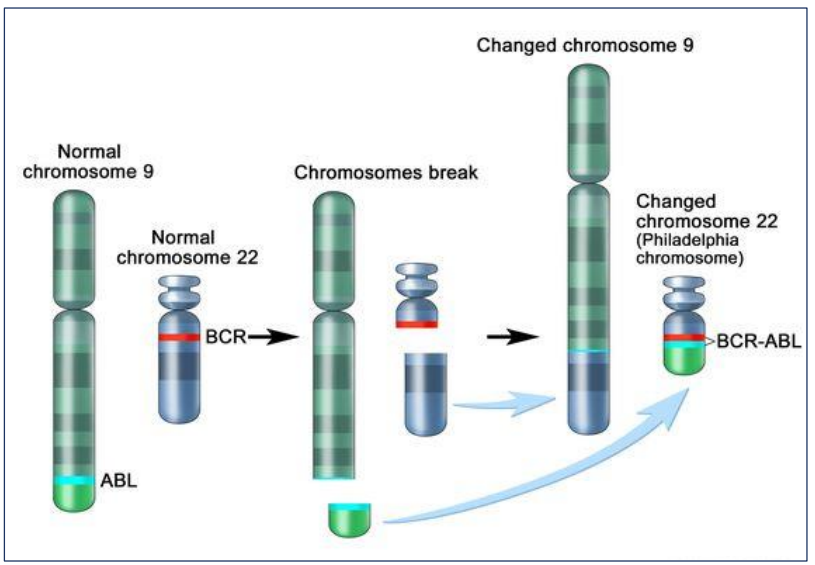
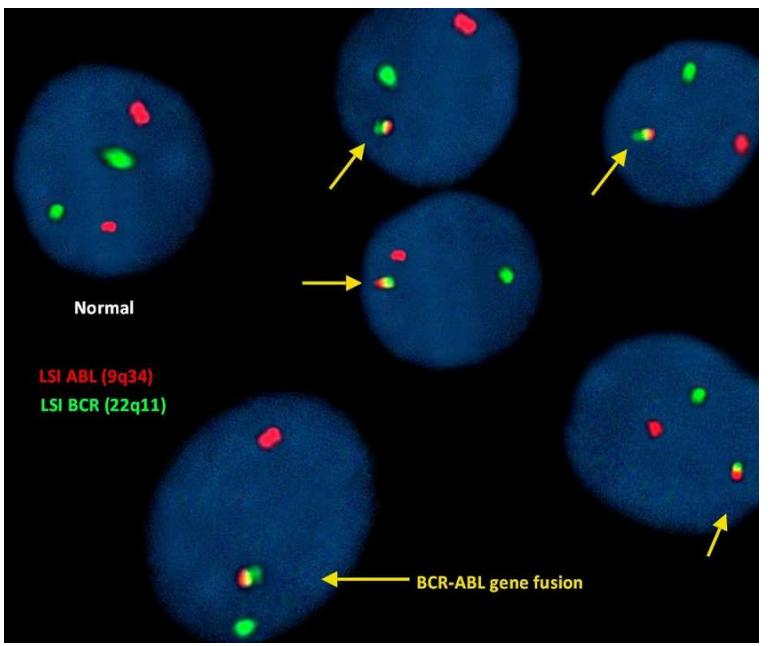
Hu Zhoa et al. J. Gene Med. 2021;(23), e3276

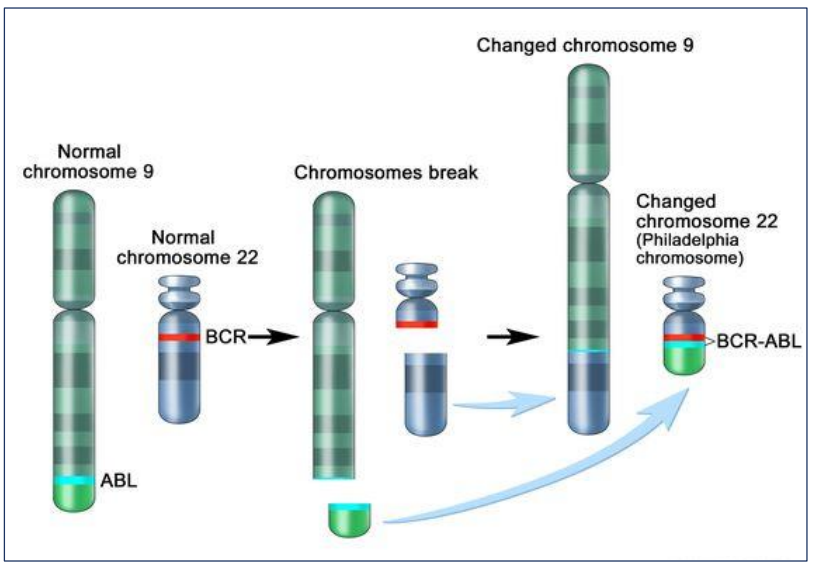
BCR::ABL1 FUSION GENE

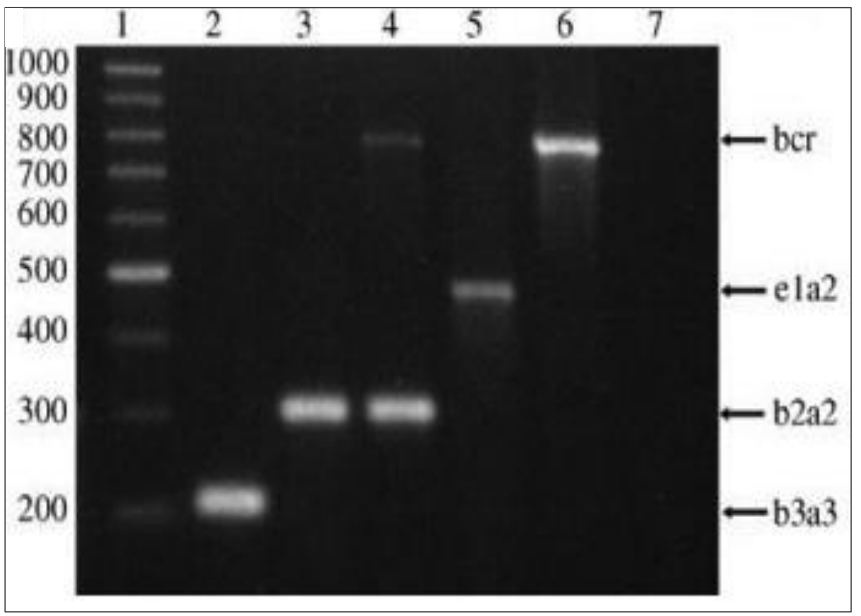




FISH

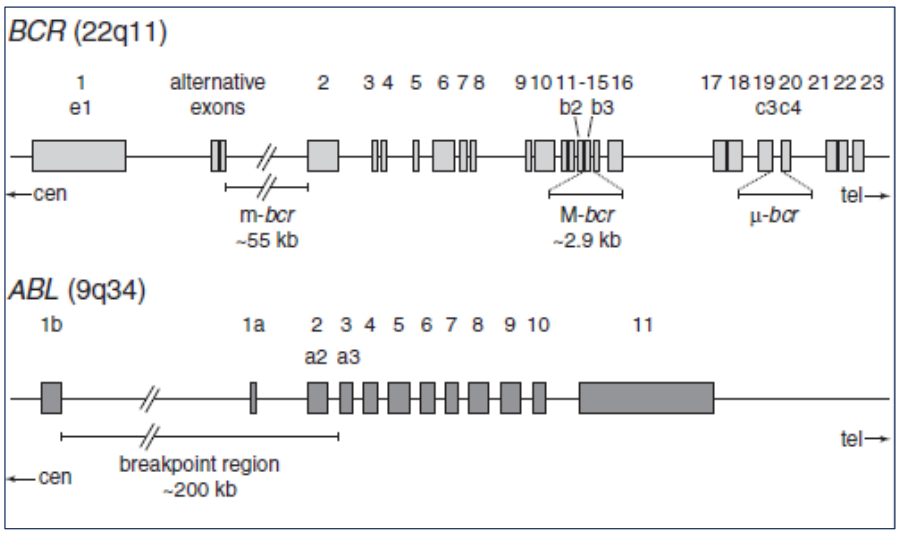
BCR::ABL1 FUSION GENE

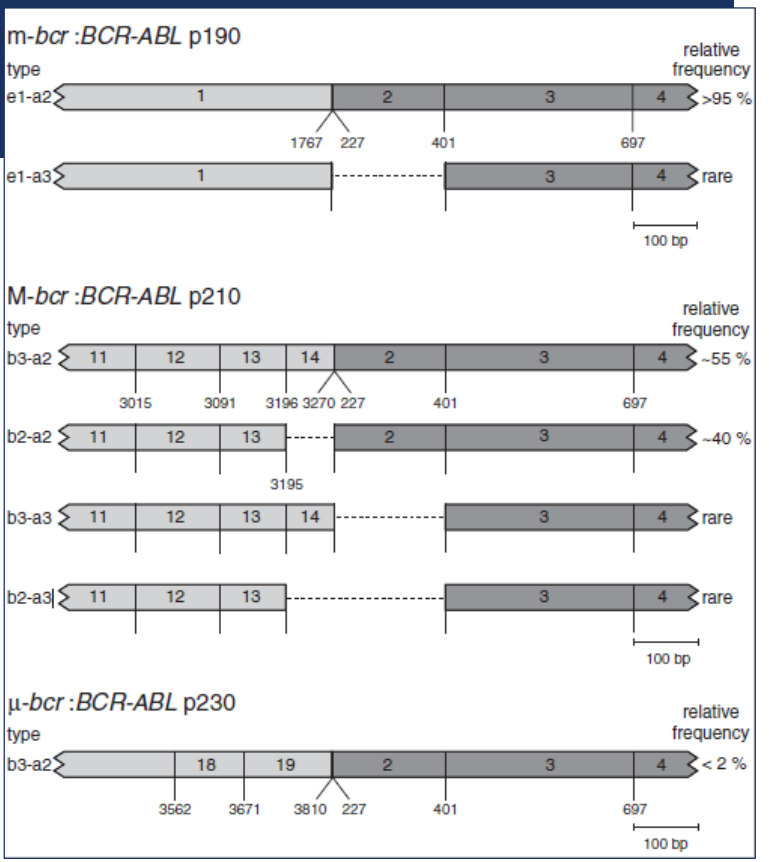




QUALITATIVE PCR

BCR::ABL1 FUSION GENE

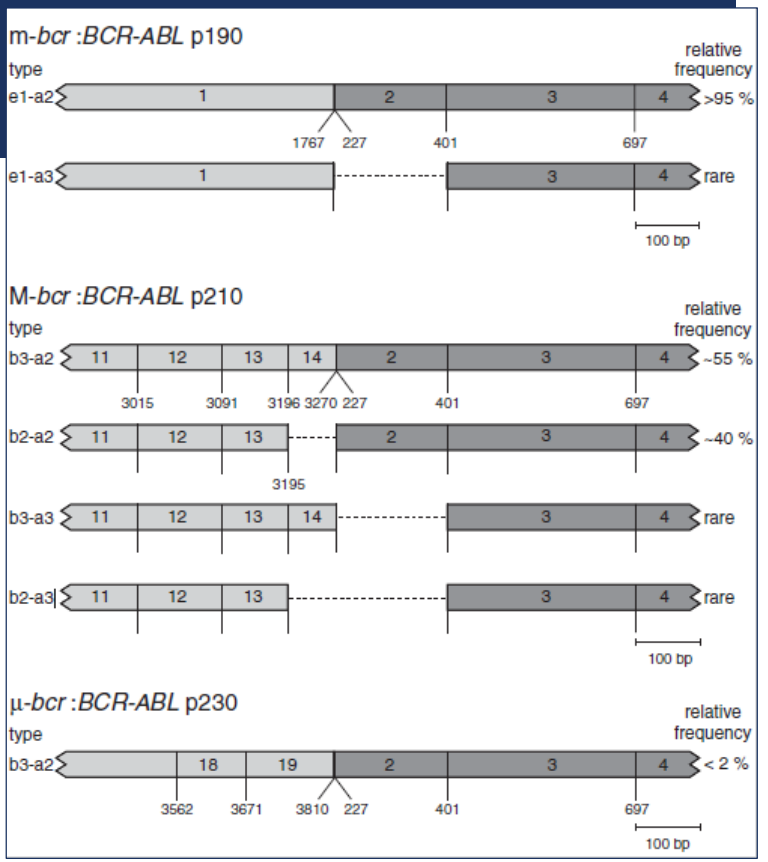




BCR::ABL1 FUSION GENE

p190 in CML: a minor Breakpoint with a major impact

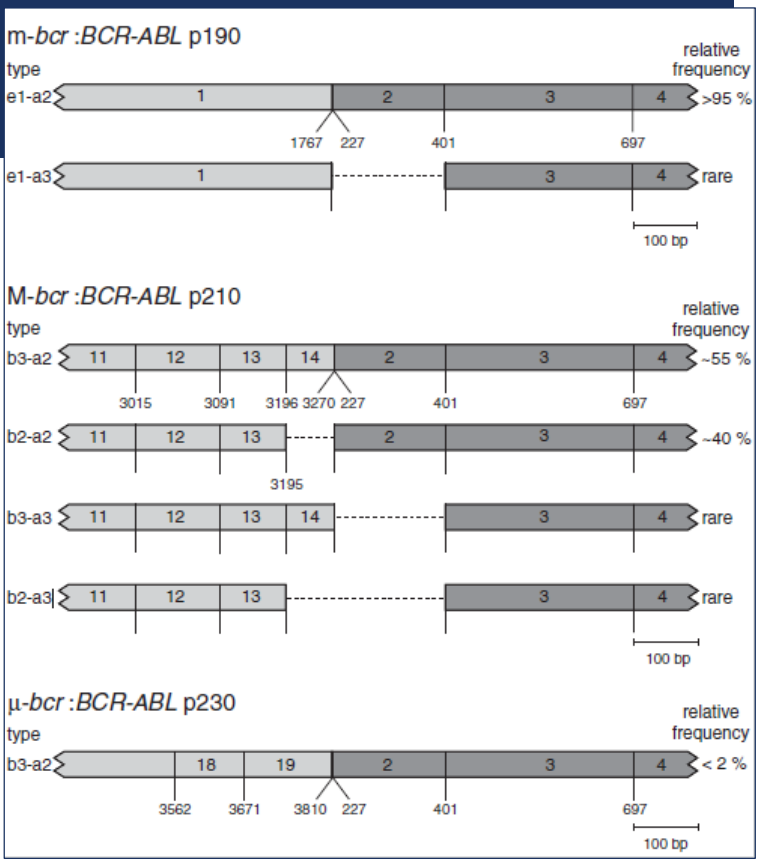
- 1-2% CML patients
- associated with distinct features like monocytosis
- frequent additional cytogenetic abnormalities at diagnosis
- should be considered as a high-risk group (treatment failure and progression)



BCR::ABL1 FUSION GENE

p210 in CML

- meta-analysis: 54,034 patients from 34 studies
- e14a2 is the more common transcript type
- e14a2 transcript is prevalent in females
- clinical impact e13a2 / e14a2?

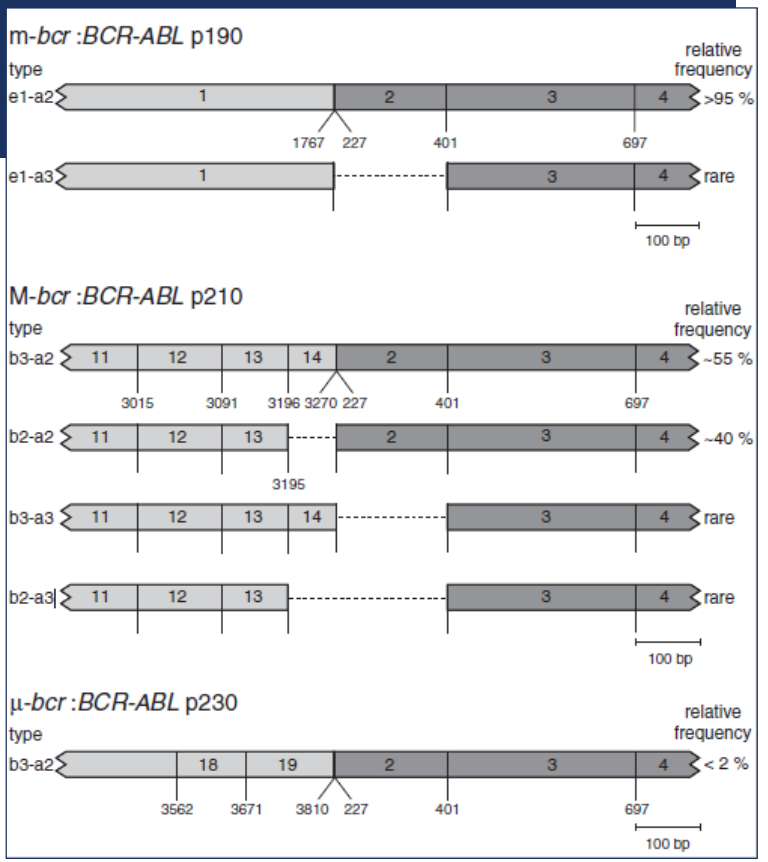


Ghalesardi OK *et al.* Leukemia Research 2021

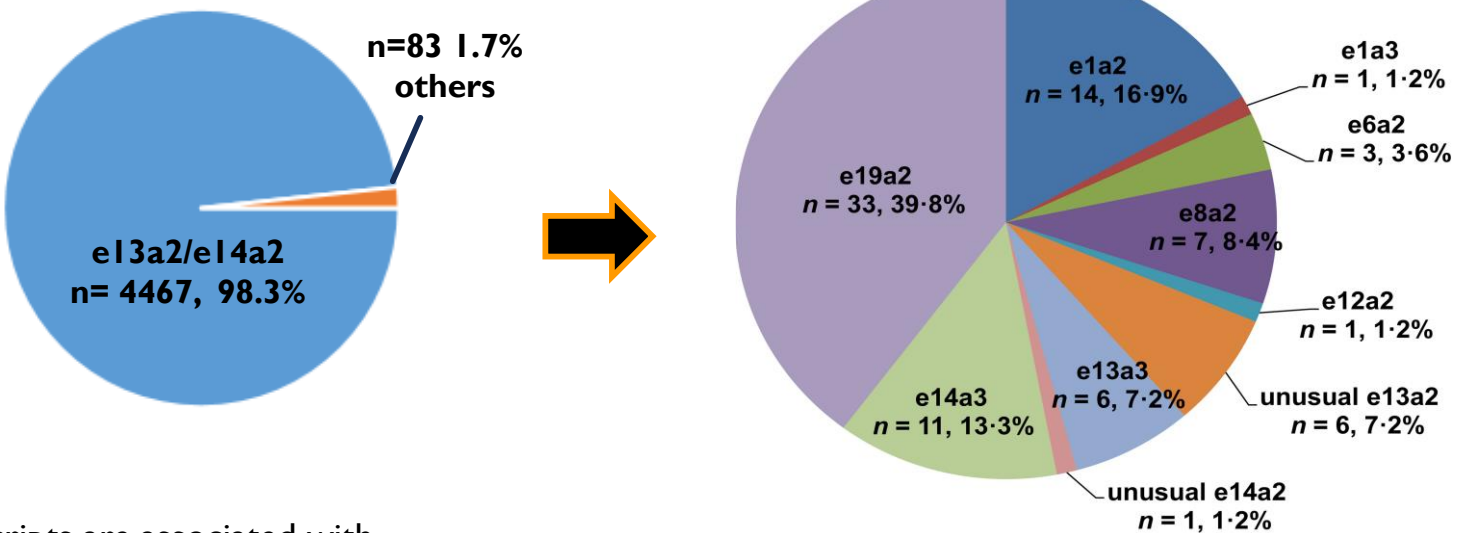
BCR::ABL1 FUSION GENE

p230 in CML

- CML with marked thrombocytosis



DISTRIBUTION OF RARE BCR::ABL1 TRANSCRIPTS IN CML

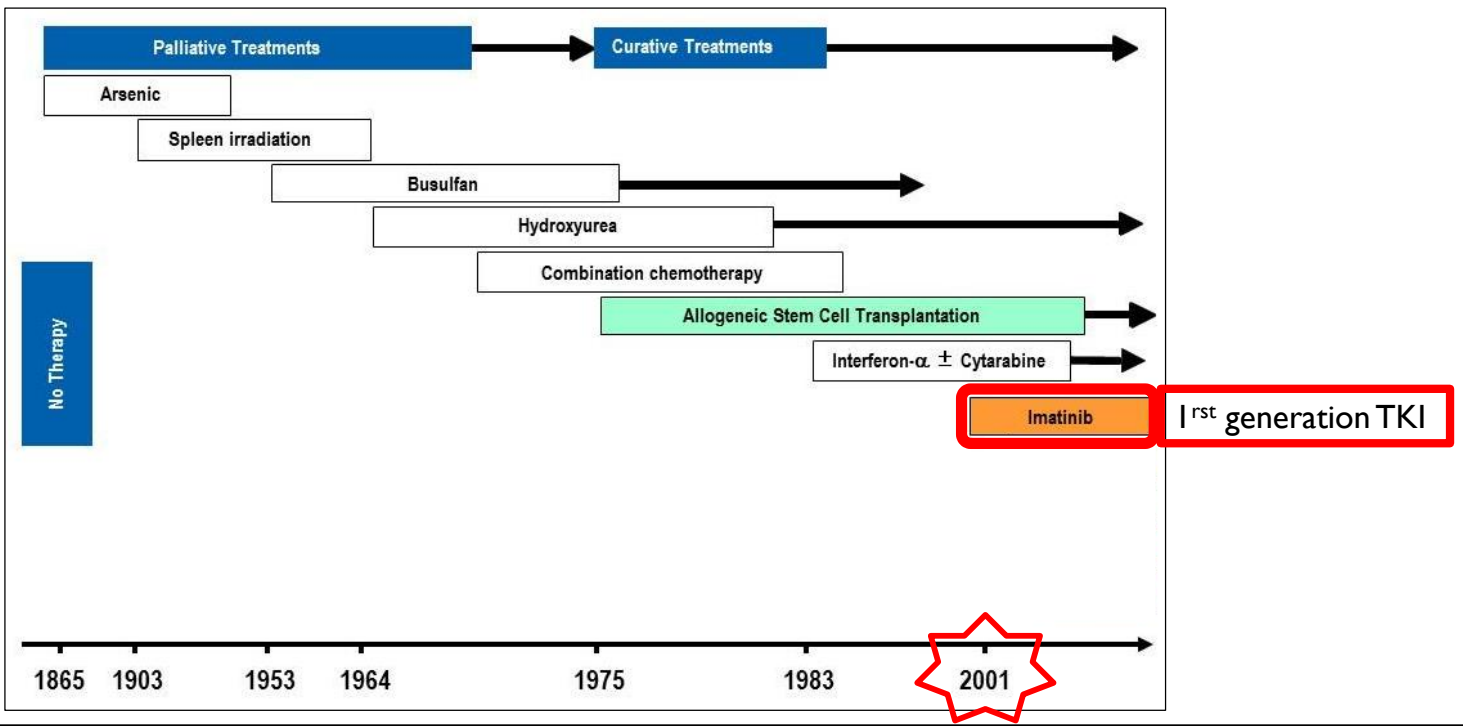


Rare transcripts are associated with

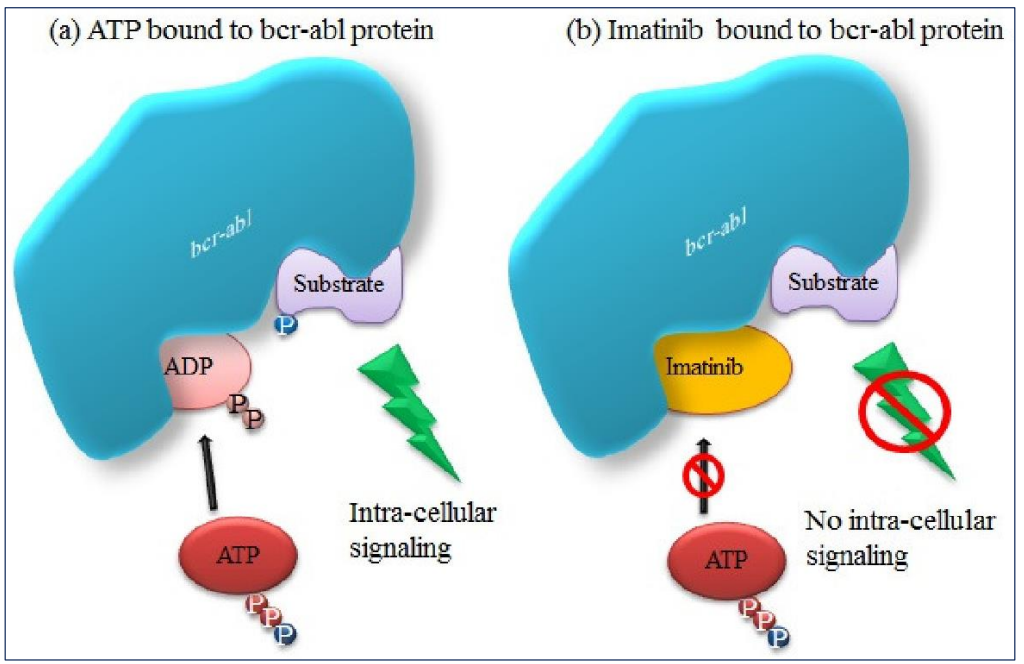
- Sex (females > males)
- Age (children/adolescents < elderly)

Qin YZ *et al.* Br J Haematol, (2018)
Baccarani M *et al.* Leukemia (2019)

TREATMENT


Palliative Treatments
Curative Treatments
Arsenic
Spleen irradiation
Busulfan
Hydroxyurea
Combination chemotherapy
Allogeneic Stem Cell Transplantation
Interferon-α ± Cytarabine
Imatinib
No Therapy
1865
1903
1953
1964
1975
1983
2001
I rst generation TKI

TREATMENT



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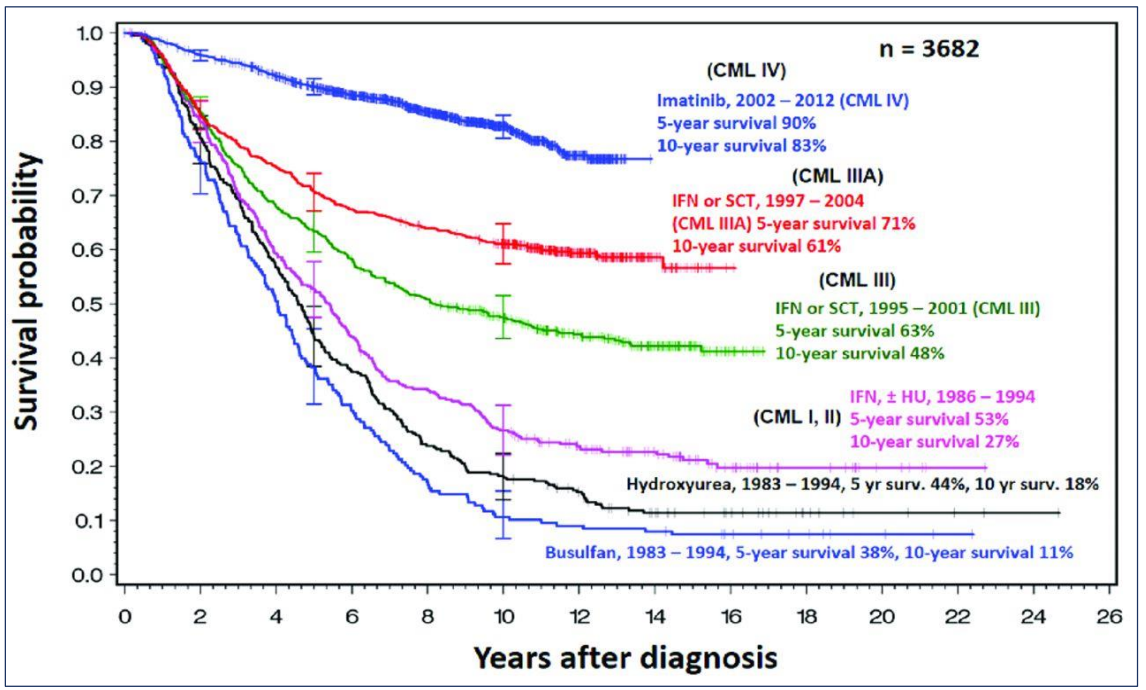
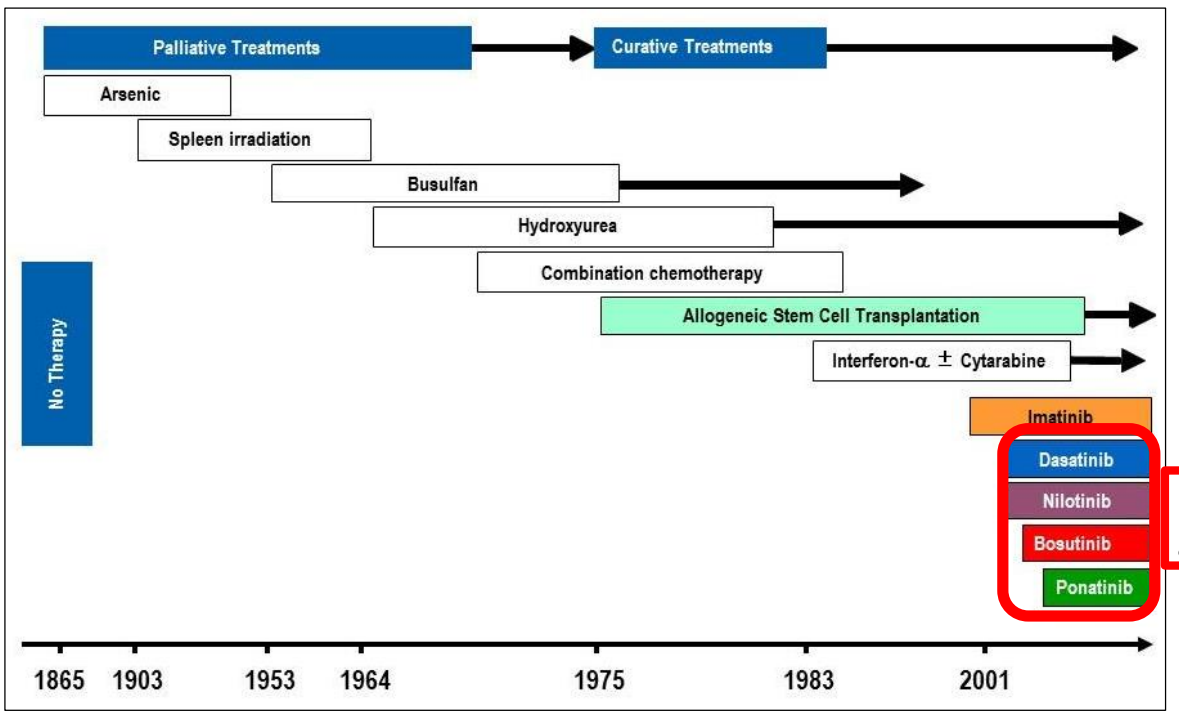
TREATMENT



Hehlmann R et al, Haematologica, 2016

TREATMENT


Palliative Treatments
Curative Treatments
Arsenic
Spleen irradiation
Busulfan
Hydroxyurea
Combination chemotherapy
Allogeneic Stem Cell Transplantation
Interferon-α ± Cytarabine
Imatinib
Dasatinib
Nilotinib
Bosutinib
Ponatinib
No Therapy
1865
1903
1953
1964
1975
1983
2001
2nd and 3rd generation TKI

DIAGNOSTIC WORKOUT AND MONITORING

Recommendations for assessment of response and monitoring

	Baseline (diagnostic work-up)	To assess the response	To monitor the response and the treatment
Blood counts and differential	Yes ⇒ **HR?**	Every 15 days until a CHR without significant cytopaenias has been achieved	Every 3 months
BM, cytology	Yes	No	No
BM, karyotype	Yes	At 3 and 6 months	Then every 6 months until CCyR has been achieved
Blood, iFISH	No	No	Only if cytogenetics of BM metaphases cannot be analysed or is normal and molecular response cannot be assessed
Blood, RT-PCR (qualitative)	Yes	No	No
Blood, qRT-PCR (quantitative, BCR–ABL %)	No	Every 3 months	Every 4–6 weeks in first year after treatment discontinuation
Mutational analysis	Only in AP or BP	No	Only in the case of failure

Hochhaus et al. Clin Pract Guid Ann Onc. (2017), Suppl 4

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BM, karyotype	Yes ⇒ **CyR?**	At 3 and 6 months	Then every 6 months until CCyR has been achieved
Blood, FISH	No	No	Only if cytogenetics of BM metaphases cannot be analysed or is normal and molecular response cannot be assessed
Blood, RT-PCR (qualitative)	Yes	No	No
Blood, qRT-PCR (quantitative, BCR–ABL %)	No	Every 3 months	Every 4–6 weeks in first year after treatment discontinuation
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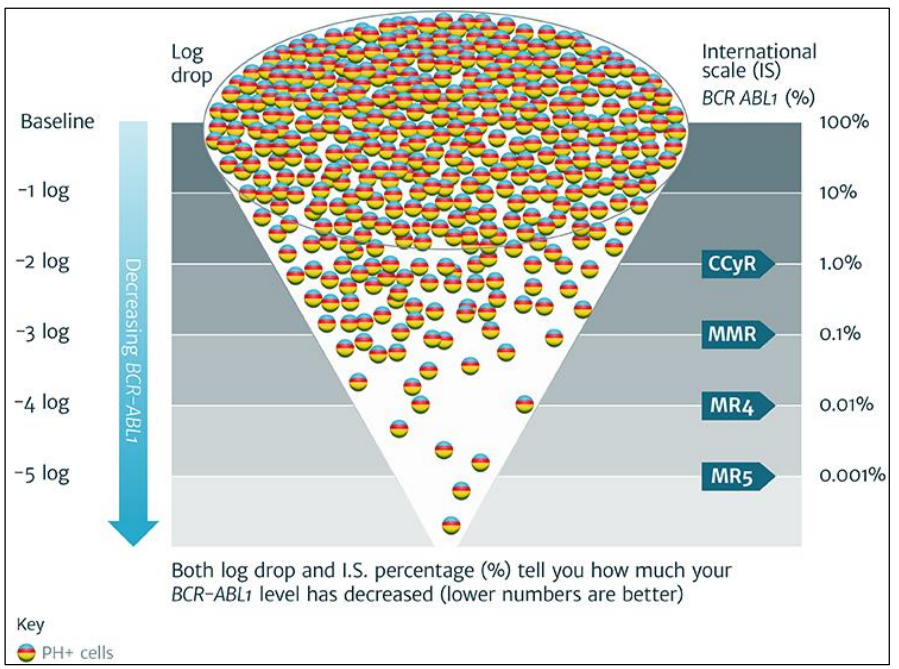
%IS BCR::ABL1 TRANSCRIPT LEVEL



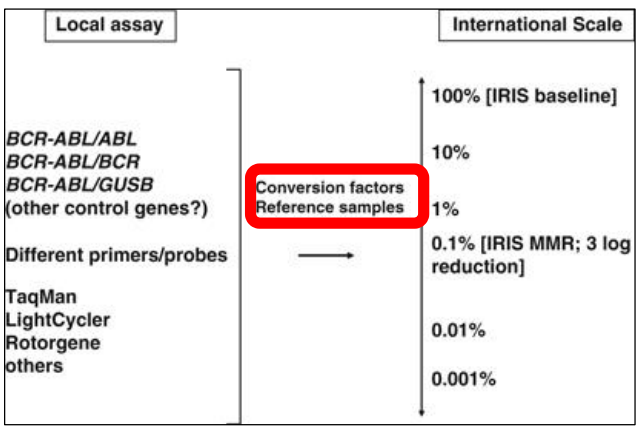
IRIS trial (2000)

- 30 diagnostic blood samples
- measured by 3 laboratories: Adelaide, Mannheim and Hammersmith
- the median value = baseline reference value and defined as 100% IS
- results reported in 1 log reductions from this baseline

%IS BCR::ABL1 TRANSCRIPT LEVEL

Two possible ways of calculating / standardize to the IS

1. **According to the conversion factor (CF)**



- many sample exchanges between laboratories
- time-consuming
- laborious

2. **Using the BCR-ABL1 reference standard method**

- commercially available

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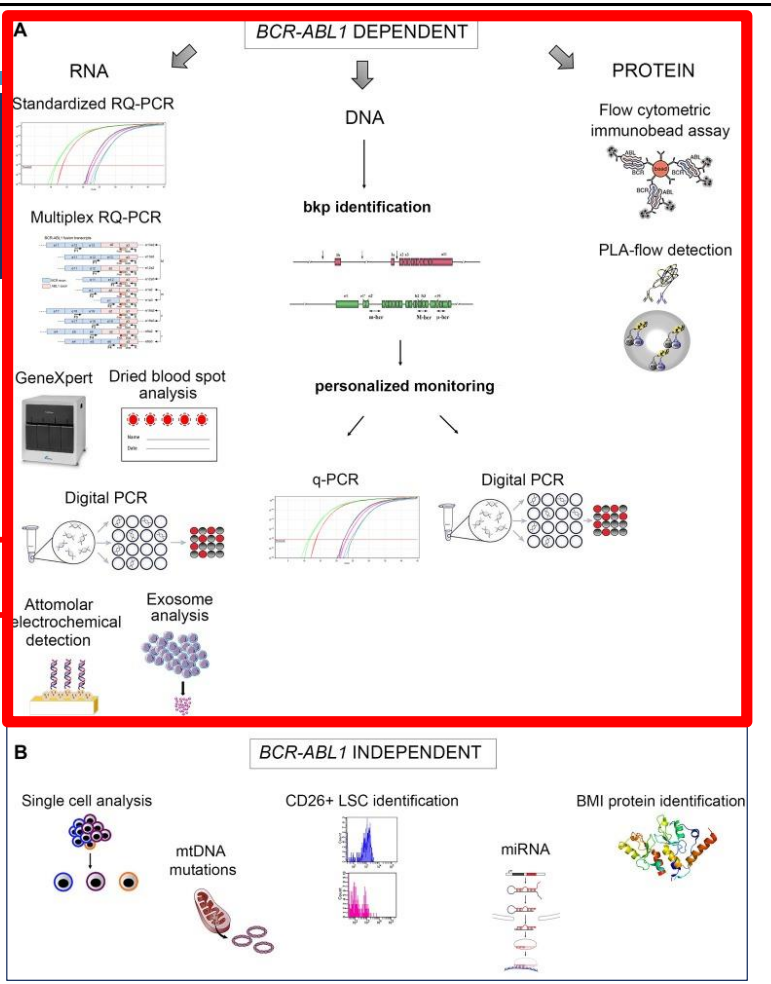
MONITORING

Methods for CML MRD monitoring.
The strategies are based on:

(A) the identification of *BCR::ABL1* fusion

(B) the detection of molecular markers independent from *BCR::ABL1*



Cumbo C *et al.* Cancer Management and research. 2020:12: 3175-89

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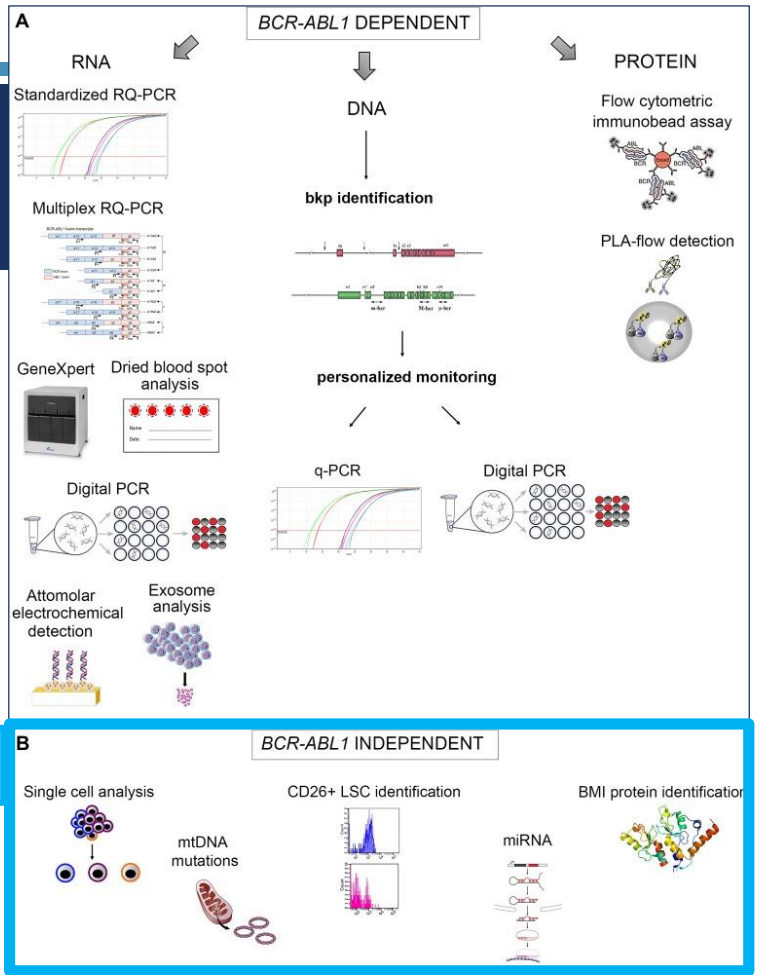

Cumbo C *et al.* Cancer Management and research. 2020:12: 3175-89

UK NEQAS
Leucocyte Immunophenotyping

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

BCR::ABL1 Major Quantification Programme

Kit/Method Data Summary

Method	Returns
Cepheid GeneXpert Ultra BCR-ABL assay	86
In-house protocol (EAC)	46
Qiagen (formerly Ipsogen) IS MMR Kit	38
In-house protocol	20
In-house (EAC-modified)	17
Qiagen (formerly Ipsogen) Fusion Quant Kit	14
QIAGEN Ipsogen BCR-ABL1 Mbcr RGQ RT-PCR	11
BCR-ABL P210 ELITe MGB Kit (Elitech Group)	7
Biorad CE-IVD QXDx BCR-ABL IS Kit	5
Other	4
Asuragen Quantidex qPCR BCR-ABL1 IS Kit	3
Bioclarma SensiQuant P210 Kit	2
Asuragen QuantideX qPCR BCRABL IS Kit	2
Entrogen BCR-ABL P210 (Mbcr) One-Step Detection	2

Control Gene Data Summary

Method	Returns
ABL1	244
GUSB	13
BCR	2

Instrument Data Summary

Method	Returns
Cepheid GeneXpert	87
Qiagen Rotorgene	34
Roche LC 480	31
ABI 7500	30
ABI QuantStudio 5	12
Biorad CFX96	9
ABI QuantStudio 7	8
Biorad QX200 Droplet Digital PCR	7
ABI 7900HT	6
ABI 7300	5
Corbett Rotorgene	5
ABI Step One Plus	5
Roche LC 2.0	4
ABI Vii A7	4
ABI 7500 FastDx	4
Roche Lightcycler	2
COBAS z480	2

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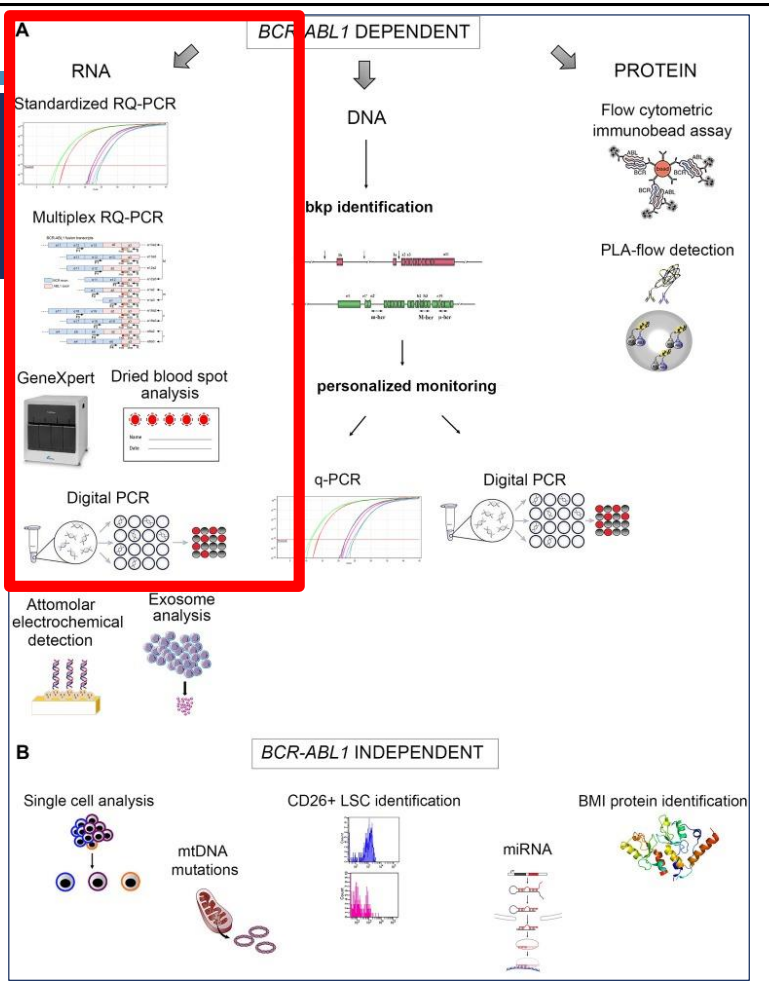
MONITORING

Method	Pros	Cons
RT-qPCR	Widely available Internationally standardized	Poor sensitivity and low precision at low levels of target Poor robustness Standard curve required
dPCR	More sensitive and accurate Enables the detection of as little as 1 copy of BCR-ABL1 transcript Performs an absolute quantification of the target without the need for a standard curve	Not yet widely available Not yet standardized

Soverini S. *et al.* J. of Clin Med. (2020)



Cumbo C *et al.* Cancer Management and research. 2020:12: 3175-89

MILESTONES 1ST AND 2ND-LINE TREATMENT (ELN 2020)

Continue current treatment

		Optimal	Warning	Failure
	Baseline	NA	High-risk ACA, high-risk ELTS score	NA
EMR	3 months	≤10%	>10%	>10% if confirmed within 1–3 months
	6 months	≤1%	>1–10%	>10%
MMR	12 months	≤0.1%	>0.1–1%	>1%
	Any time	≤0.1%	>0.1–1%, loss of ≤0.1% (MMR)[a]	>1%, resistance mutations, high-risk ACA

ACA additional chromosome abnormalities in Ph+ cells

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From: ELN 2020 recommendations for treating CML

TKI DISCONTINUATION

Table 7 Cumulative incidence of deep molecular response (MR^4 and $MR^{4.5}$) with imatinib, nilotinib, and dasatinib by 5 and 10 years.

Study		5 years (%)	10 years (%)
CML-Study IV[a], [36, 37]	Imatinib MR^4	68	81
	Imatinib $MR^{4.5}$	53	72
ENESTnd[b], [41, 52]	Nilotinib MR^4	66	73
	Nilotinib $MR^{4.5}$	54	64
	Imatinib MR^4	42	56
	Imatinib $MR^{4.5}$	35	45
Dasision[c], [40]	Dasatinib $MR^{4.5}$	42	NA
	Imatinib $MR^{4.5}$	33	NA

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From: European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia

TKI DISCONTINUATION

Criteria to guide selection of patients suitable for TFR attempt

Criteria	Green	Yellow	Red
Institutional criteria met (per table 1)	Yes	-	No
Sokal score at diagnosis	Non-high	High	-
BCR-ABL transcript at diagnosis	Typical - B2A2 or B3A2 (e13a2 or e14a2)	Atypical, but can be accurately quantified	Not quantifiable
CML past history	CP only	Resistance or KD mutation	Prior AP or BC
Response to first line TKI therapy	Optimal	Warning	Failure
Duration of all TKI therapy	> 8 years	3–8 years	< 3 years
Depth of deep molecular response	MR4.5	MR4.0	Not in MR4.0
Duration of deep molecular response monitored in a standardized laboratory	> 2 years	1–2 years	< 1 year

All green: strong recommendation to consider TKI withdrawal

Any yellow: only consider TKI withdrawal in high priority circumstances (eg. planned pregnancy)

Any red: TKI withdrawal not recommended except in clinical trials

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Hughes T *et al.* Blood (2017)

TKI DISCONTINUATION

Mandatory requirements	• CML in first CP only (data are lacking outside this setting)
	• Motivated patient with structured communication
	• Access to high quality quantitative PCR using the IS with rapid turn-around of PCR test results
	• Patient's agreement to more frequent monitoring after stopping treatment; monthly for the first 6 months, every 2 months for months 6–12, and every 3 months thereafter
Minimal requirements (stop allowed)	• First-line therapy or second-line if intolerance was the only reason for changing TKI
	• Typical e13a2 or e14a2 BCR–ABL1 transcripts
	• Duration of TKI therapy >5 years (>4 years for 2GTKI)
	• Duration of DMR (MR^4 or better) >2 years
	• No prior treatment failure
Optimal requirements (stop recommended for consideration)	• Duration of TKI therapy >5 years
	• Duration of DMR > 3 years if MR^4
	• Duration of DMR > 2 years if $MR^{4.5}$

From: ELN 2020 recommendations for treating CML

TKI DISCONTINUATION

Results of TKI discontinuation

- disease recurred in about 50-60% of patients
- recurrence mostly within the first 6-8 months (=> persistence of LSC)
- disease rarely comes back after one year TKI discontinuation
- patients can usually restart TKI treatment
- 90%– 95% of patients achieve undetectable levels of disease again

NOMENCLATURE (ART 33 TER)

Hematologische aandoeningen: follow-up

Pseudocode/ID	omschrijving	Code art 33ter/niveau	Het aantal keer dat de pseudocode per tijdvak van één jaar opnieuw kan aangerekend worden
594753 - 594764	Opsporen van BCR/ABL1 (Philadelphia chromosoom) bij monitoring van chronische myeloïde leukemie of Ph+ acute lymfatische leukemie	594075 - 594086 (Niveau 2 follow-up)	4
594871 - 594882	Opsporen van t(15;17) PML-RARa translocatie bij monitoring van acute promyelocytaire leukemie	594075 - 594086 (Niveau 2 follow-up)	4
595092 – 595103	Opsporen van BCR/ABL1 (Philadelphia chromosoom) bij monitoring van behandelingsvrije remissie bij CML in het 1ste jaar na TKI stop	594075 - 594086 (Niveau 2 follow-up)	12
595114 – 595125	Opsporen van BCR/ABL1 (Philadelphia chromosoom) bij monitoring van behandelingsvrije remissie bij CML in het 2de jaar na TKI stop	594075 - 594086 (Niveau 2 follow-up)	6

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MILESTONES 1ST AND 2ND-LINE TREATMENT (ELN 2020)

Consider possible TKI switch

	Optimal	Warning	Failure
Baseline	NA	High-risk ACA, high-risk ELTS score	NA
3 months	≤10%	>10%	>10% if confirmed within 1–3 months
6 months	≤1%	>1–10%	>10%
12 months	≤0.1%	>0.1–1%	>1%
Any time	≤0.1%	>0.1–1%, loss of ≤0.1% (MMR)[a]	>1%, resistance mutations, high-risk ACA

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From: ELN 2020 recommendations for treating CML

MILESTONES 1ST AND 2ND-LINE TREATMENT (ELN 2020)

	Optimal	Warning	Failure
Baseline		KINETICS OF EARLY TREATMENT RESPONSE	NA
3 months			>10% if confirmed within 1–3 months
6 months	≤1%	>1–10%	>10%
12 months	≤0.1%	>0.1–1%	>1%
Any time	≤0.1%	>0.1–1%, loss of ≤0.1% (MMR)[a]	>1%, resistance mutations, high-risk ACA

ACA additional chromosome abnormalities in Ph+ cells

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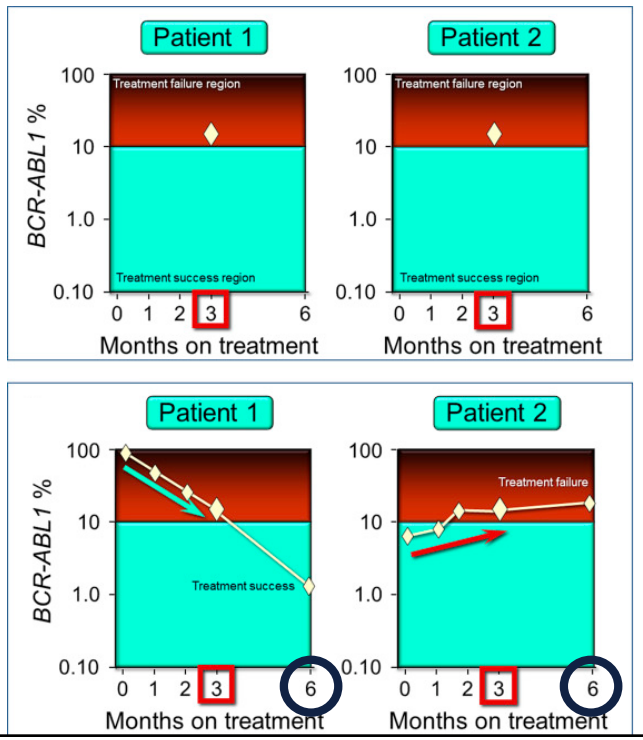
From: ELN 2020 recommendations for treating CML

RESPONSE KINETICS



- wide range of pre-imatinib *BCR::ABL1* levels
- IS, although very good for classifying response for most patients, does not suit every situation
- role for examining actual pre-imatinib level to assess trend of response at 3 months of TKI (kinetics not yet incorporated in follow-up recommendations)

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Brandford S, Best Pract & Res Clin Hem: 2016, 284-94

MILESTONES 1ST AND 2ND-LINE TREATMENT (ELN 2020)

Change current treatment

	Optimal	Warning	Failure
Baseline	NA	High-risk ACA, high-risk ELTS score	NA
3 months	≤10%	>10%	>10% if confirmed within 1–3 months
6 months	≤1%	>1–10%	>10%
12 months	≤0.1%	>0.1–1%	>1%
Any time	≤0.1%	>0.1–1%, loss of ≤0.1% (MMR)[a]	>1% resistance mutations, high-risk ACA

ACA additional chromosomal abnormalities in Ph+ cells

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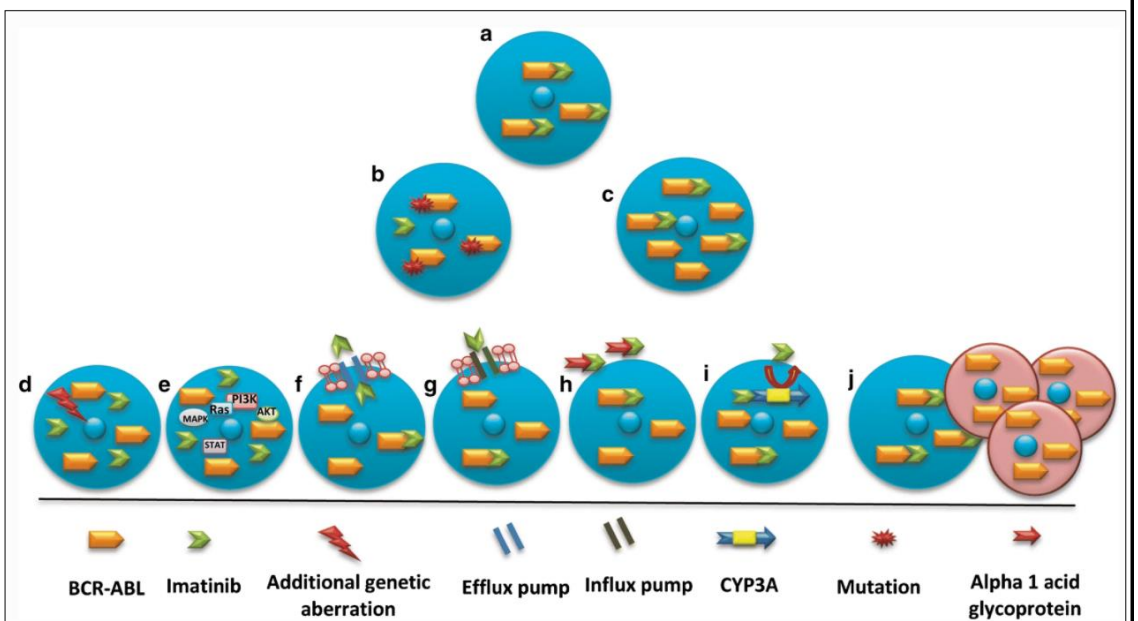
From: ELN 2020 recommendations for treating CML

TKI RESISTANCE

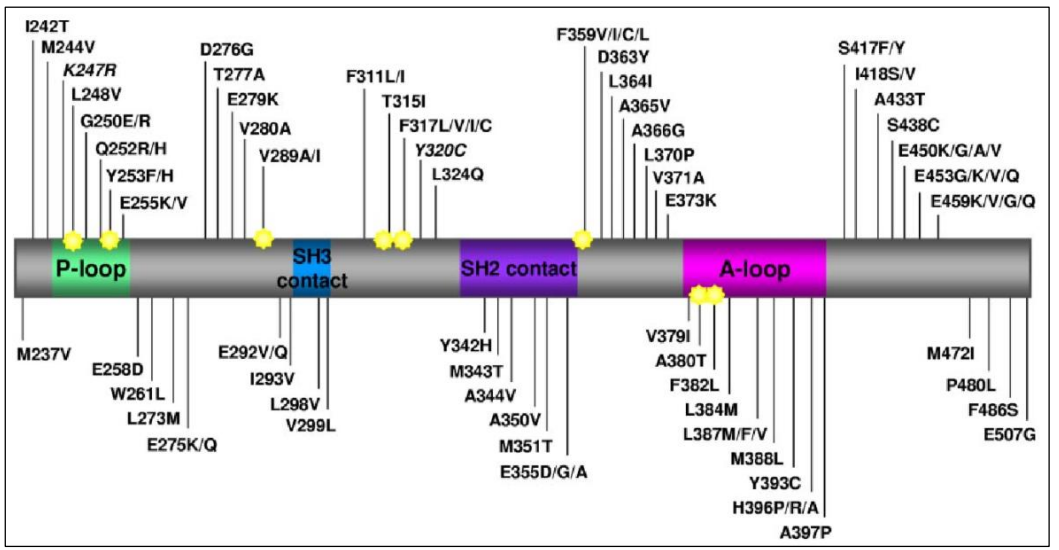
BCR::ABL1 dependent
ABL1 kinase domain (KD) mutations
Increased BCR-ABL1 expression
BCR::ABL1 independent
Poor compliance
Drug influx and efflux
Activation of alternative signaling pathways
Plasma TKI concentration
Insensitivity of quiescent stem cells



Yaghmaie M. et al, Curr Hematol Malig Rep. 2019

BCR::ABL1 KD MUTATIONS

- In case of resistance for first line TKI: 1/3
- In case of resistance to second or subsequent-line therapy: up to 50%
- In AP or BC patients: 70-80%
- Multiple mutations are often detectable (one or multiple low mutants detectable in addition to dominant mutants)



Soverini S. *et al.* J. Hemat. & Oncol. (2019)
Soverini S *et al.* Blood (2011)

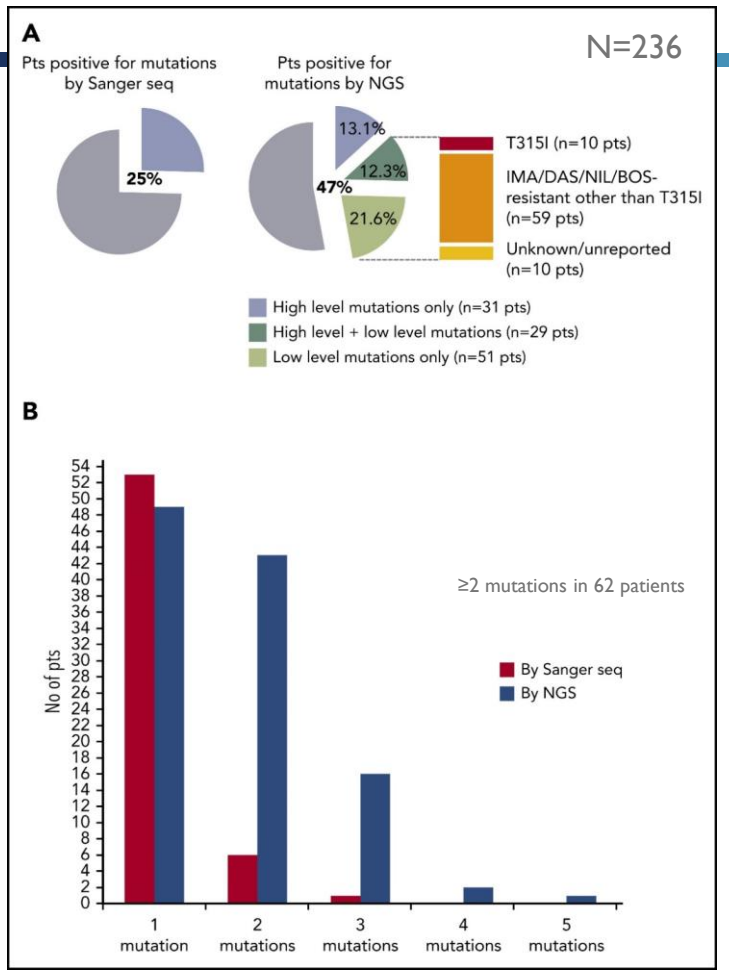
BCR::ABL1 KD MUTATIONS

- Detection method
  - Sanger sequencing
  - NGS
  - dPCR

Table 2. Summary of the main advantages and disadvantages of old (Sanger sequencing) versus novel (NGS and dPCR) technologies for BCR-ABL1 KD mutation testing.

Method	Pros	Cons
Sanger sequencing	Widely available Easy to use	Poor sensitivity
NGS	More sensitive than Sanger sequencing Enables to scan the entire KD for any mutation Enables clonal analysis in case of multiple mutations falling within the same sequence reads (discrimination between compound and polyclonal mutations)	Not yet widely available Requires pooling of a minimum of 8–10 samples to be cost-effective Labor-intensive Not yet standardized RT-PCR and sequencing errors generate background "noise" at lower levels of sensitivity Chemistries and instruments still evolving
dPCR	Cheap, fast, and simple Has the greatest sensitivity	Can be implemented only for a limited number of mutations Not yet standardized May confirm the presence of compound mutations only if the mutation partners are already known and, hence, specific probes can be designed and used

Soverini S. *et al.* J. Hemat. & Oncol. (2019)
Soverini S. *et al.* J. of Clin Med. (2020)



blood®
Volume 134, Supplement 1, 13 November 2019, Page 661

632.Chronic Myeloid Leukemia: Therapy

Detection of Actionable BCR-ABL1 Kinase Domain (KD) Mutations in Chronic Myeloid Leukemia (CML) Patients with Failure and Warning Response to Tyrosine Kinase Inhibitors (TKIs): Potential Impact of Next-Generation Sequencing (NGS) and Droplet Digital PCR (ddPCR) on Clinical Decision Making

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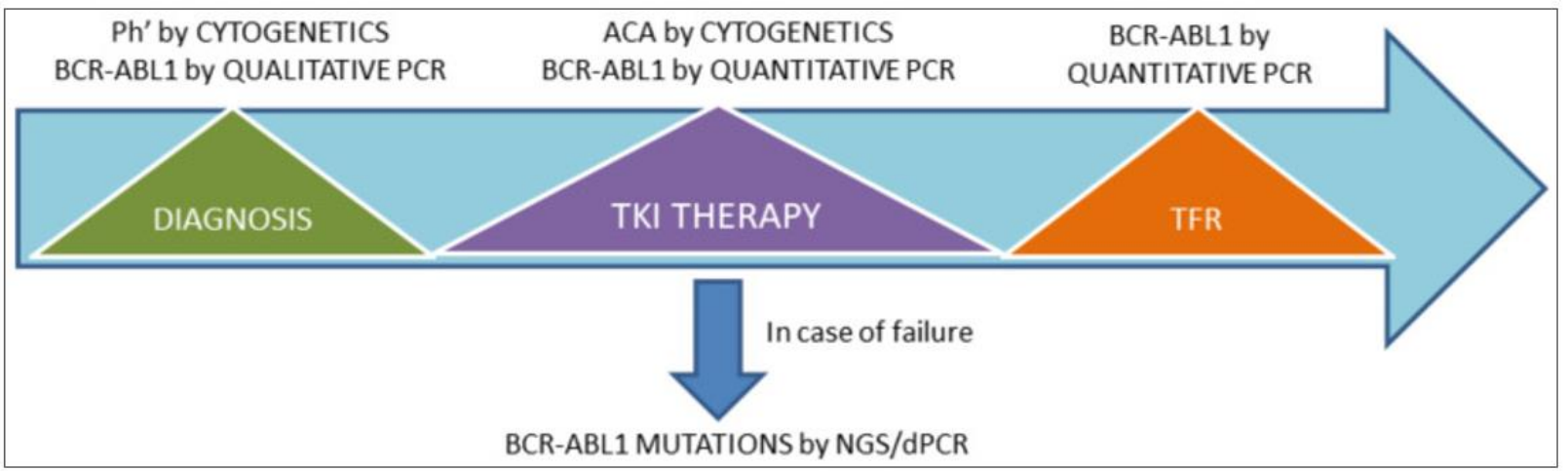
Soverini S. *et al.* Blood (2020)
Soverini S. *et al.* AHS (2019)

FLOW CHART OF ROUTINE ASSESSMENTS IN CML (2020 ELN RECOMMENDATIONS)



51

Soverini S. *et al.* J. Clin. Med. (2020)

TKI RESISTENCE - NGS TESTING FOR BCR::ABL1 KD MUTATIONS

Indications for the use of NGS testing in chronic phase CML

- in patients with failure[a] response to TKI therapy, irrespective of the TKI
- in patients with warning[a] response to TKI therapy, irrespective of the TKI

Indications for the use of NGS testing before allogeneic stem cell transplant (allo-SCT)

- *BCR-ABL1* KD mutation status by NGS testing before allo-SCT may provide useful information regarding when post-transplant TKI therapy should be reinstated. Patients who do not have *BCR-ABL1* KD mutation results by NGS available at the time of transplant should be tested[b]

Indications for the use of NGS testing in advanced CML phases

- all patients with advanced phase (AP or BC) either at diagnosis or during therapy

Indications for the use of NGS testing after TKI therapy discontinuation

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- in patients relapsing after a TFR attempt if they fail to re-achieve MMR within 3–6 months after TKI re-treatment

Soverini S. *et al.* J. Hemat. & Oncol. (2019)

BCR::ABL1 KD MUTATIONS

Table 1 List of *BCR-ABL1* KD mutations poorly sensitive to imatinib, dasatinib, nilotinib, bosutinib, and ponatinib based on the integration of published studies (2001–2018) reporting the mutation status of TKI-resistant patients and experimental data

Mutations poorly sensitive to imatinib	M237V, I242T, **M244 V**, K247R, L248V, **G250E**, G250R, Q252R, **Q252H**, **Y253F**, **Y253H**, **E255K**, **E255V**, E258D, W261L, L273M, E275K, E275Q, **D276G**, T277A, E279K, V280A, V289I, V289I, V289A, E292Q, E292V, I293V, L298V, **F311L**, F311I, **T315I**, **F317L**, F317V, F317I, F317C, Y320C, L324Q, Y342H, M343T, A344V, A350V, **M351T**, E355D, **E355G**, E355A, **F359V**, F359I, F359C, F359L, D363Y, L364I, A365V, A366G, L370P, V371A, E373K, V379I, A380T, F382L, **L384M**, **L387F**, L387V, M388L, **H396R**, **H396P**, H396A, A397P, S417F, S417Y, I418S, I418V, A433T, S438C, E450K, E450G, E450A, E450V, E453G, E453A, E453K, E453V, E453Q, **E459K**, E459V, E459G, E459Q, M472I, P480L, **F486S**
Mutations poorly sensitive to dasatinib	V299L, T315I, T315A, F317L, F317V, F317I, F317C
Mutations poorly sensitive to nilotinib	Y253H, E255K, E255V, T315I, F359V, F359I, F359C
Mutations poorly sensitive to bosutinib[a]	E255V, E255K, V299L, T315I
Mutations poorly sensitive to ponatinib	T315M, T315L

[a]In contrast to the other second-generation TKIs, there is still limited data available on mutations associated with clinical resistance to bosutinib in vivo. In vitro data suggest that the E255K and, to a lesser extent, the E255V might be poorly sensitive to bosutinib
TKI tyrosine kinase inhibitor
The most frequent imatinib-resistant mutations are highlighted in boldface

Soverini S. *et al.* J. Hemat. & Oncol. (2019)

Table 5 Recommended tyrosine kinase inhibitors in case of BCR-ABL1 resistance mutations.

T315I	Ponatinib
F317L/V/I/C, T315A	Nilotinib, bosutinib[a], or ponatinib
V299L	Nilotinib or ponatinib
Y253H, E255V/K, F359V/I/C	Dasatinib, bosutinib[a], or ponatinib

[a]There are limited data available regarding mutations associated with clinical resistance to bosutinib in vivo. Some in vitro data suggest that the E255K and, to a lesser extent, the E255V mutation, might be poorly sensitive to bosutinib.

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From: ELN 2020 recommendations for treating CML