1ST INTERNATIONAL CONFERENCE ON

Ph+Leukemias

Bologna, Royal Hotel Carlton **September 29-30, 2025**

ADVANCED PHASE CML

CARMEN FAVA

University of Turin

Disclosures Fava Carmen

Company name	Research support	Employee	Consultant	Stockholder	Speakers	Advisory board	Other
Novartis	x				x		
Pfizer	x				x		
Incyte					x	x	
GSK					x		
Gentili					x		
Blueprint					x		
Ascentage						x	

Mechanisms of Progression

- The molecular mechanisms underlying progression to BP-CML are likely multifactorial.
- While CP-CML results from acquisition of BCR-ABL1 in a primitive haemopoietic stem cell, in BP progenitor cells acquire self-renewal potential and undergo differentiation arrest.
- Progenitors in BP-CML have more stem cell-like properties, with upregulation of β-catenin and C-MYC activity.

Jamienson CH et al. N Engl J Med

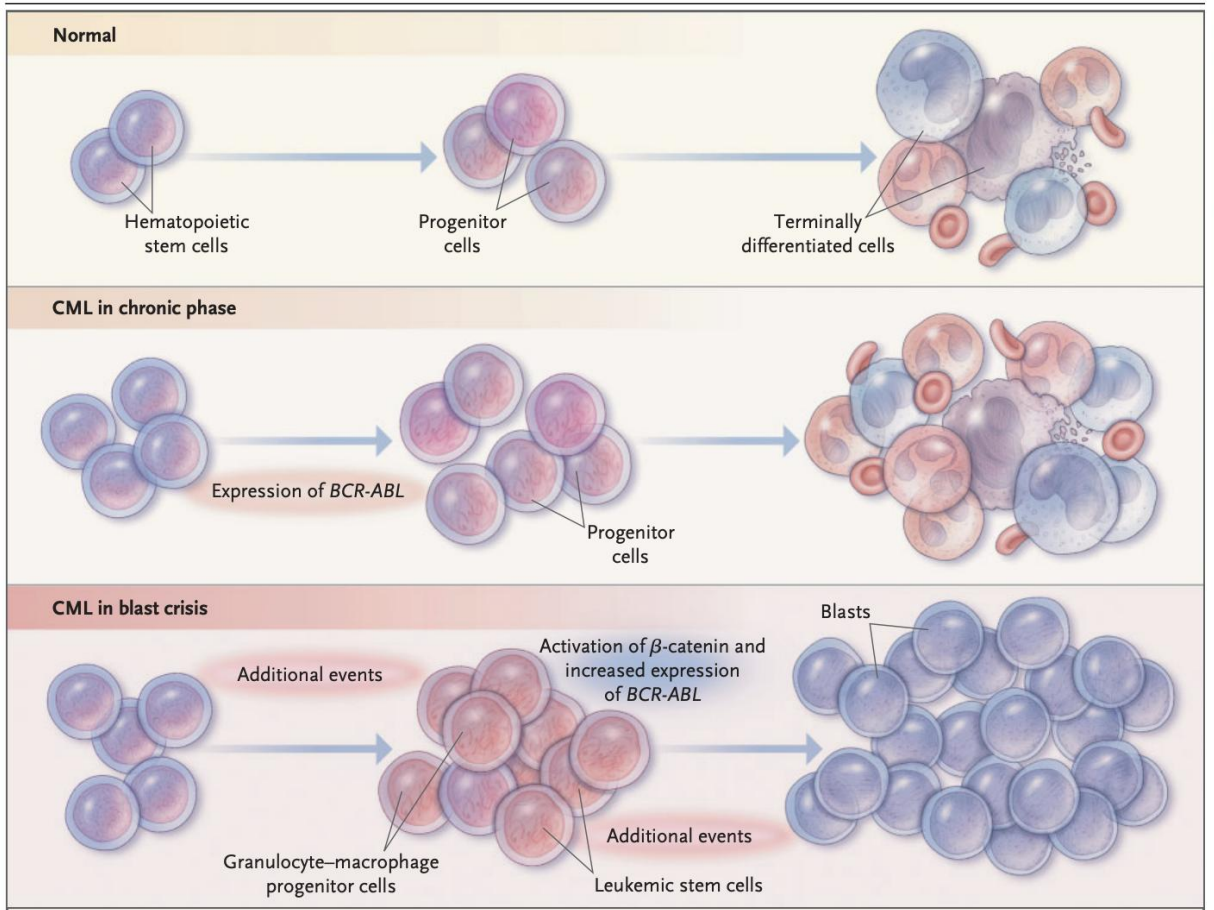
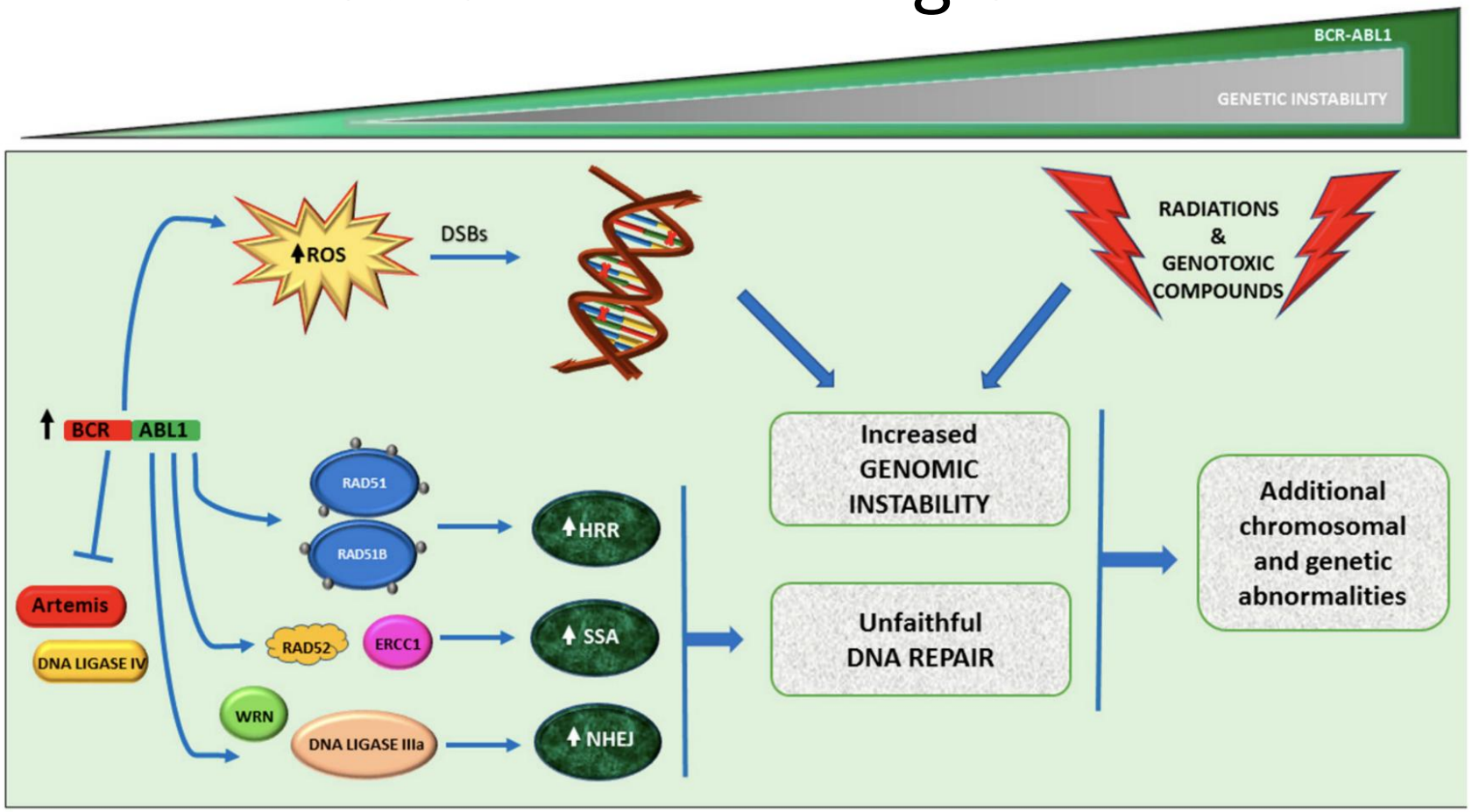


Figure 5. Model of the Role of Activated β-Catenin in the Progression of CML.

Unlike the progenitor pool in healthy subjects, in patients with chronic-phase CML, cells within the progenitor pool have an increased proliferative capacity owing to elevated expression of *BCR-ABL*. This increased proliferative capacity leads to a myeloproliferative syndrome but does not affect the pathways of cell death and differentiation. Progression to blast crisis results from additional events, including the activation of β-catenin in the granulocyte–macrophage progenitor population, increasing their proliferative and self-renewal capacity and possibly allowing them to become leukemic stem cells. Avoidance of cell death, evasion of innate and adaptive immune responses, and a block in differentiation must also occur for CML to progress.

Mechanisms of Progression



- High levels of BCR::ABL1 are responsible for the generation of reactive oxygen species and stimulate unfaithful DNA repair mechanisms, thus leading to increase DNA damage.
- This phenomenon causes genomic instability and a high mutation burden, including acquisition of ACAs and molecular lesions.

Bavaro I et al. Int J Mol Sci 2019; Copland M Br J Haematol 2022

Incidence of Progression

Table 1. Incidence of progression to accelerated and/or blast phase in the major frontline TKI studies in chronic phase CML

Clinical trial (follow-up in years)	Frontline TKI (dose)			
	Imatinib	Nilotinib	Dasatinib	Bosutinib
IRIS[42] (10 years)	7% (400 mg)			
TOPS[43] (42 months)	4.5% (400 mg)/2.5% (800 mg)			
CML-IV[44] (10 years)	6% (400 mg)/5% (800 mg)			
TIDEL-II[45] (40 months)	3.5% (600 mg)			
ENESTnd[46] (10 years)	8.5% (400 mg)	4% (300 mg BD)/2% (400 mg BD)		
ENESTfirst (24 months)		0.6% (300 mg BD)		
DASISION[47] (5 years)	7% (400 mg)		5% (100 mg)	
BFORE[48] (5 years)	3% (400 mg)			2% (400 mg)

BD, twice daily.

The number of progressions has decreased with the use of first-line tyrosine kinase inhibitors, remaining below 10% with imatinib and below 5% with second-generation inhibitors.

Shanmuganathan N & Hughes T. ASH Education Program 2023

Disease phases & evolving classifications

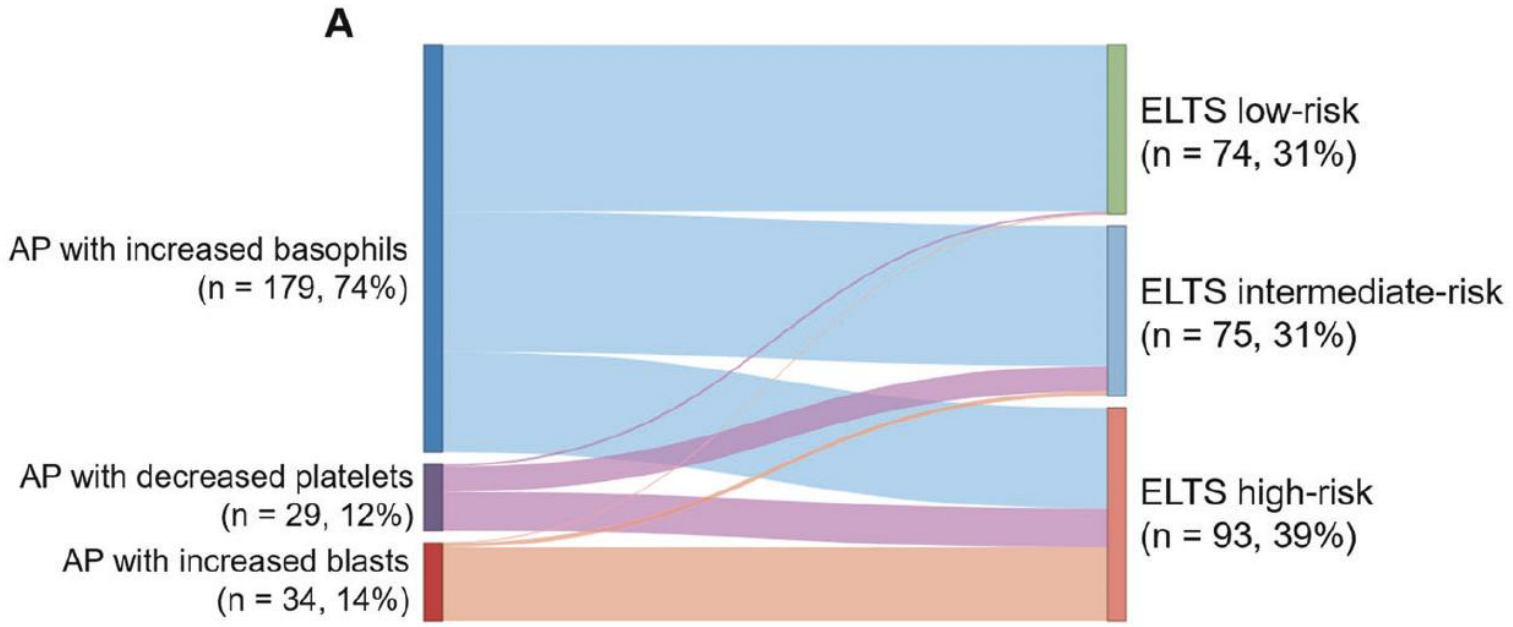
Defining the stages of CML has become more complicated with recent update to the various classification systems

- **WHO 2022 (5th ed.)**: *removed* an explicit AP category; classifies CML as **Chronic phase** or **Blast phase** (≥20% blasts or extramedullary blast proliferation; Khoury JD et al. Leukemia 2022)

- **ICC 2022**: **retains AP** with simplified criteria; **10–19% blasts** (blood or marrow) defines AP; **≥20% blasts** defines BP (Aber DA et al. Blood 2022)

- **Practical point** (2025): Clinical practice, trials, and guidelines (ELN, NCCN) still commonly speak in AP/BP terms; fear to lack criteria for identification of patients who need more potent TKI as first line therapy.

Rational for removing AP

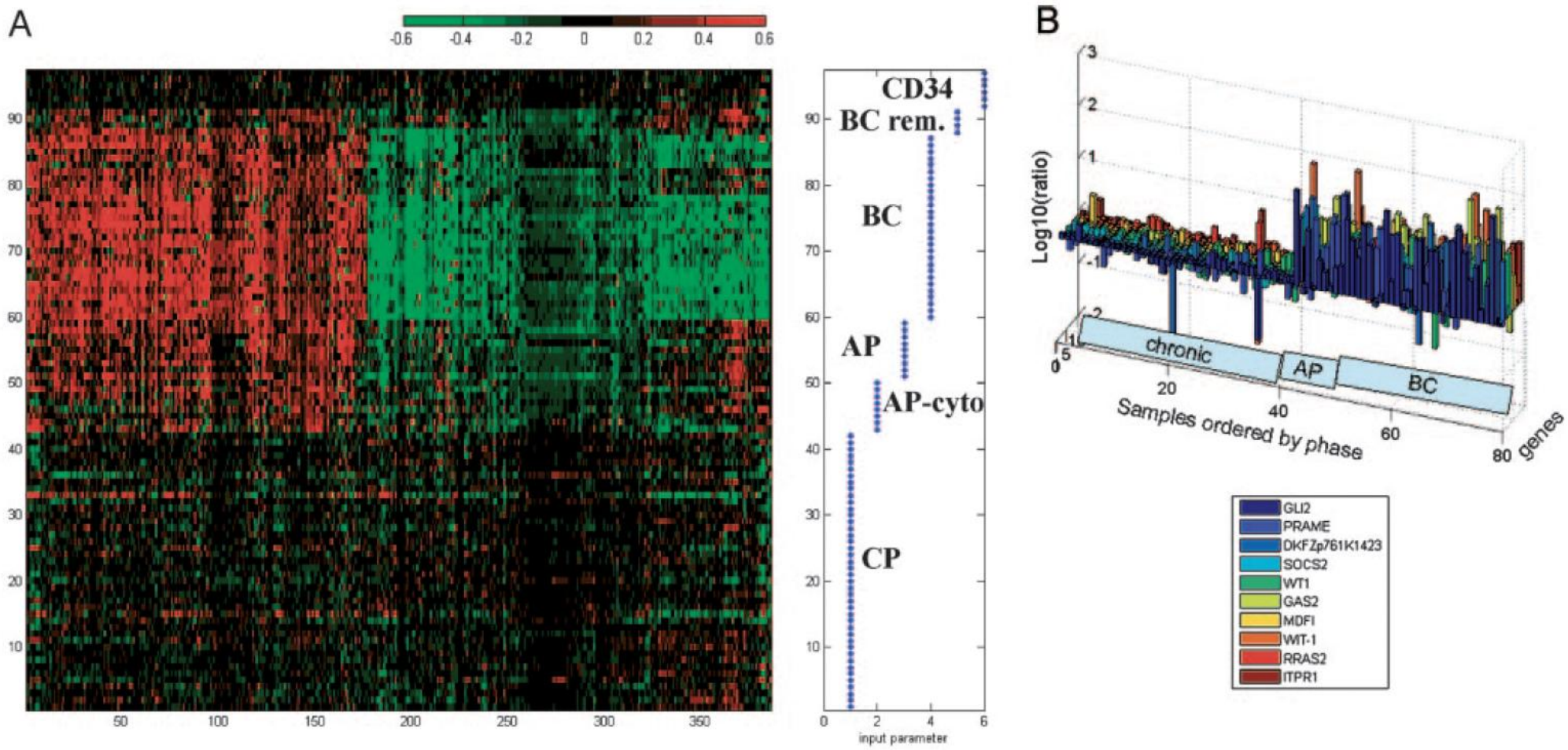


- In an analysis of > 2000 people with CML in either CP or AP at diagnosis (based on the 2020 ELN and 2022 ICC criteria) they found that most subjects classified as AP had outcomes like persons in CP identified as intermediate- or high-risk cohorts classified by the ELTS risk classification.

- Most patients treated in CP and AP are treated with single agents TKIs and the majority of APs have responses similar to CP.

Gale RP et al. Leukemia 2024; Yang S et al Leukemia 2025

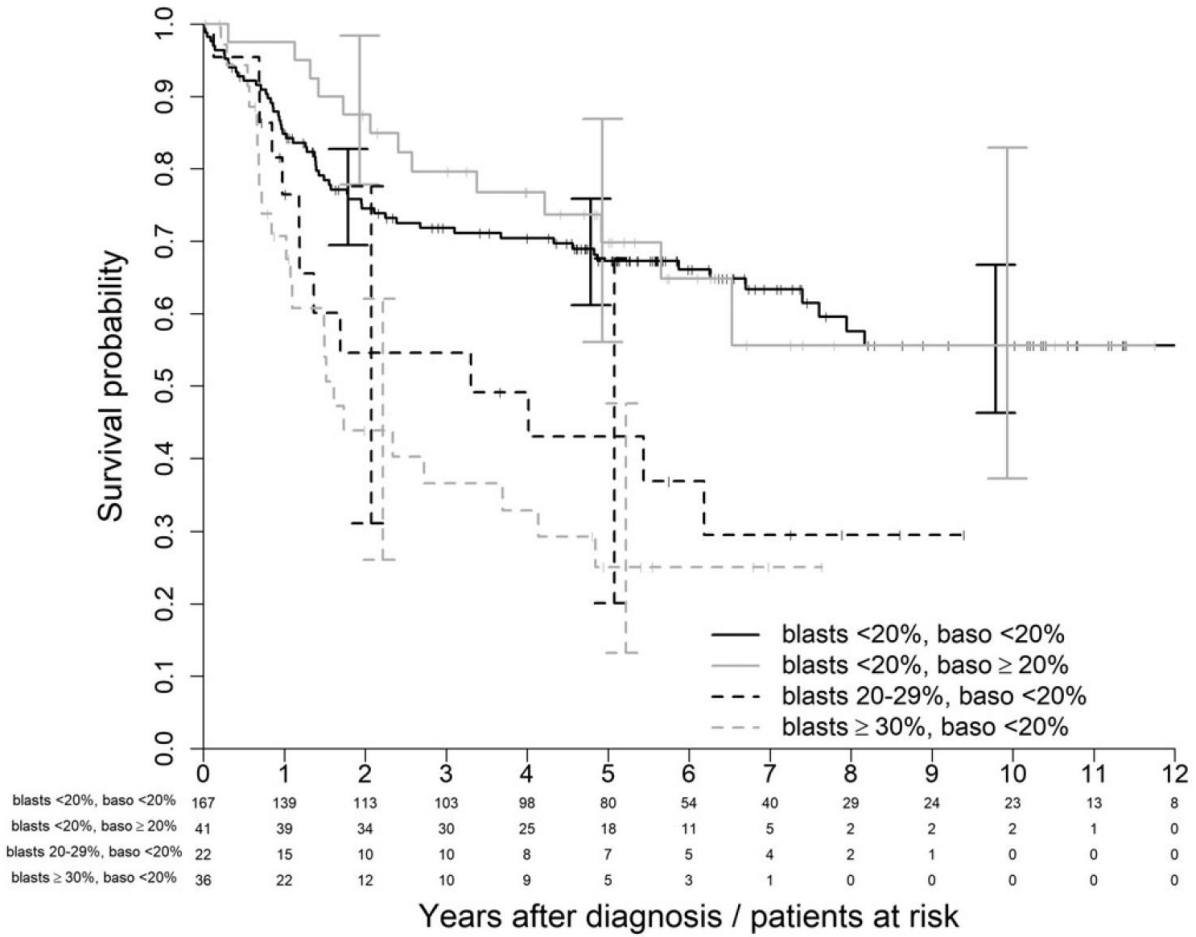
Rational for removing AP



In gene-expression analyses, CP patients differ markedly from those in BC, whereas AP patients are genetically much more similar BC.

Radich JP at al. PNAS 2006

Rational for 20% blasts cut-off



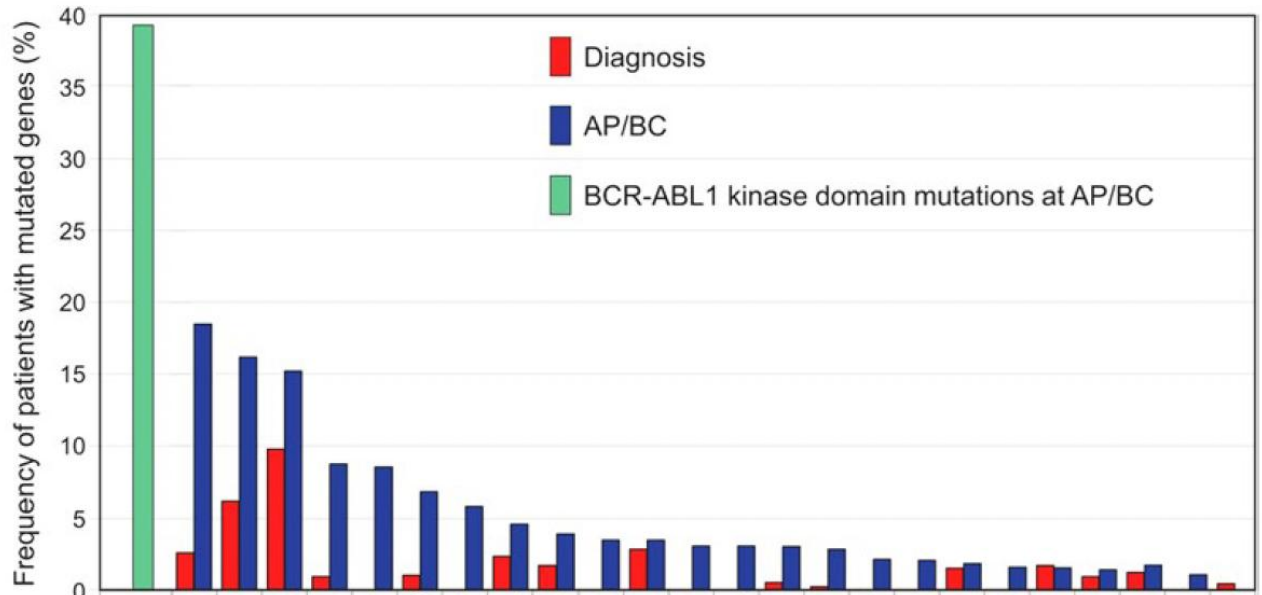
Patients with blasts between 20% and 30% have an outcome more similar to those with blasts >30% than those between 10% and 20%.

Lauseker M et al. Am J Hematol 2019

Diagnostic framework for AP and BP

- **Flow cytometry** (at diagnosis and on therapy)
  - To enable accurate enumeration of blast percentage
  - To confirm the phenotype of identified blasts
- **Cytogenetic analysis** (at diagnosis and on therapy)
  - The original ACAs are defined as trisomy 8, additional Ph translocation, isochromosome 17q, and trisomy 19.
  - Additional high-risk cytogenetic lesions, including trisomy 21, **3q26.2**, monosomy 7/7q-, 11q23, and a complex karyotype were identified as conferring an inferior OS and a higher propensity to be present at BP-CML.
- **Mutational analysis for kinase domain mutations** (at diagnosis and on therapy)
  - 80% vs 50% of patients by NGS vs conventional sanger sequencing
- Ideally: whole exome or transcriptome sequencing

Soverini et al Bolood 2020; Shanmuganathan N & Hughes T. ASH Education Program 2023; ELN 2025

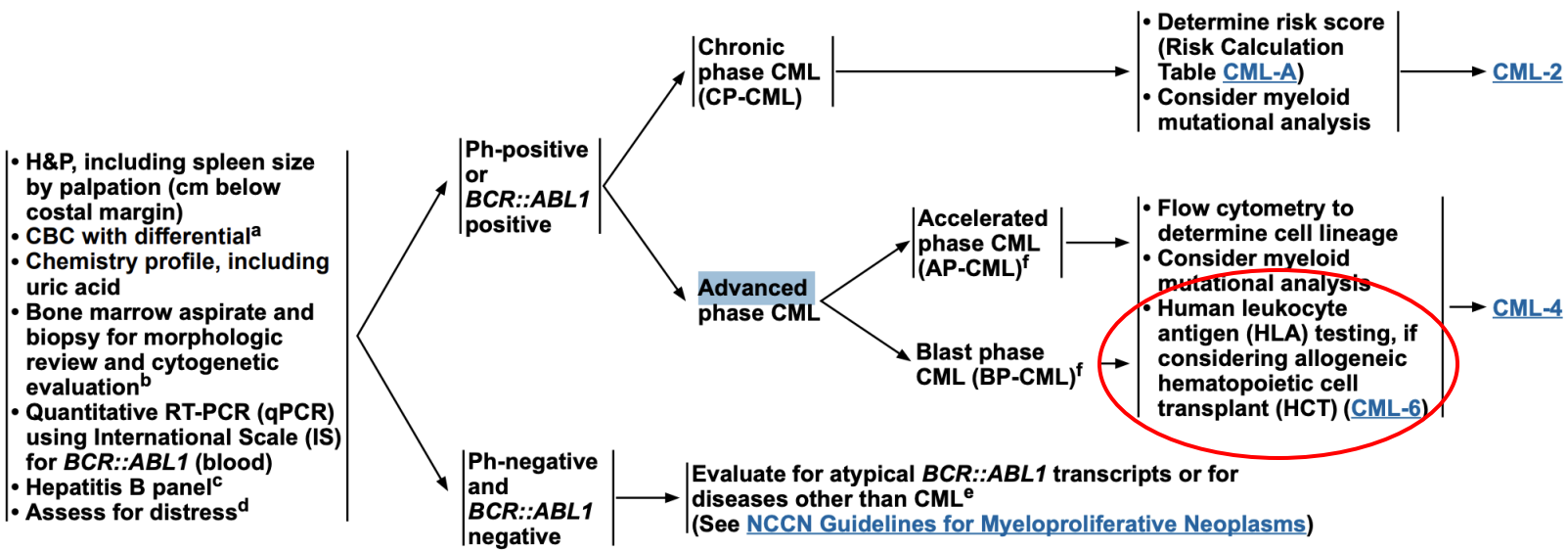


	BCR-ABL1 kinase domain	RUNX1	IKZF1 exon deletion	ASXL1	BCORL1	GATA2	TET2	WT1	DNMT3A	TP53	SETBP1	SETD1B	PHF6	BCOR	PTPN11	IDH1	IDH2	CBLB	JAK2	NRAS	KMT2D	CBL	IKZF1 SNV/indel	KRAS	EZH2
Diagnosis																									
No. of patients tested		349	49	518	109	109	439	224	348	237	209	109	209	209	209	489	489	209	323	224	333	224	333	224	348
No. with variants		9	3	50	1	0	4	0	8	4	0	3	0	0	1	1	0	0	5	0	4	2	4	0	2
%		**2.6**	**6.1**	**9.7**	**0.9**	**0**	**0.9**	**0**	**2.3**	**1.7**	**0**	**2.8**	**0**	**0**	**0.5**	**0.2**	**0**	**0**	**1.5**	**0**	**1.2**	**0.9**	**1.2**	**0**	**0.6**
AP/BC																									
No. of patients tested	89	191	106	199	58	143	165	105	66	206	58	58	66	66	67	285	285	98	111	191	66	145	126	191	67
No. with variants	35	35	17	30	5	12	11	6	3	8	2	2	2	2	2	8	6	2	2	2	1	2	1	2	0
%	**39.3**	**18.3**	**16.0**	**15.1**	**8.6**	**8.4**	**6.7**	**5.7**	**4.5**	**3.9**	**3.4**	**3.4**	**3.0**	**3.0**	**3.0**	**2.8**	**2.1**	**2.0**	**1.8**	**1.6**	**1.5**	**1.4**	**0.8**	**1.0**	**0**

Figure 2. Frequency of mutated cancer genes at diagnosis and AP/BP. The data from 15 studies of patients at diagnosis and 20 studies at AP/BP are reported where cancer genes were mutated in more than 1 patient at diagnosis and/or BP. Only genes listed in the COSMIC Cancer Gene Census are included. Adapted from Branford et al. with permission.[2]

However, a targeted approach is feasible.

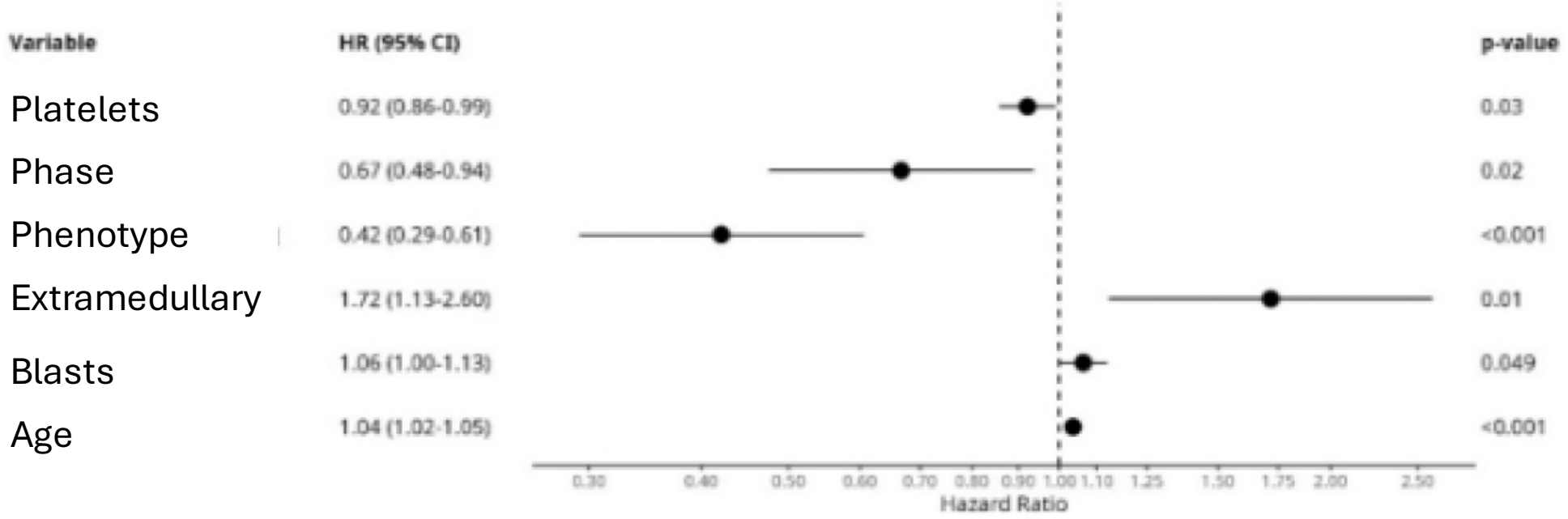
Branford S et al Leukemia 2022; Shanmuganathan N & Hughes T. ASH Education Program 2023



[a] Hydroxyurea is the preferred option (until the initiation of TKI therapy) to lower very high white blood cell (WBC) counts. Leukapheresis is rarely indicated, except for high-risk indications (eg, persistent priapism, shortness of breath, transient ischemic attack).
[b] Bone marrow cytogenetics with a minimum of 20 metaphases is useful to detect chromosomal abnormalities in addition to the Ph chromosome. The presence of major route additional chromosomal abnormalities (ACAs) in Ph-positive cells (trisomy 8, isochromosome 17q, second Ph, trisomy 19, and chromosome 3 abnormalities) may have a negative prognostic impact on survival in patients with accelerated phase. Fluorescence in situ hybridization (FISH) on the bone marrow or peripheral blood (with a minimum of 100 interphase nuclei evaluated) can be used if bone marrow cytogenetic evaluation is not possible.
[c] Hepatitis B virus reactivation has been reported in patients receiving tyrosine kinase inhibitor (TKI) therapy. However, it is not always possible to reliably estimate the frequency or establish a relationship to drug exposure because these incidences are reported voluntarily from a population of uncertain size.
[d] Refer to the NCCN Distress Thermometer and Problem List, which includes social determinants of health. See NCCN Guidelines for Distress Management (DIS-A).
[e] Consider dual fusion FISH (D-FISH) or qualitative reverse transcription polymerase chain reaction (RT-PCR) for the detection of atypical *BCR::ABL1* transcripts. See Discussion. Referral to centers with expertise in the management of rare hematologic malignancies is recommended for patients with atypical *BCR::ABL1* transcripts.
[f] Definitions of Advanced Phase CML (CML-B).

Abstract: S165

Title: DEVELOPMENT OF A PROGNOSTIC SCORING SYSTEM FOR CHRONIC MYELOID LEUKEMIA IN BLAST PHASE: INSIGHTS FROM THE EUROPEAN LEUKEMIANET BLAST PHASE REGISTRY



Micheal Lauseker, EHA 2024

240 BP from 2015 to 2023

Management and outcome of patients with chronic myeloid leukemia in blast phase in the tyrosine kinase inhibitor era – analysis of the European LeukemiaNet Blast Phase Registry

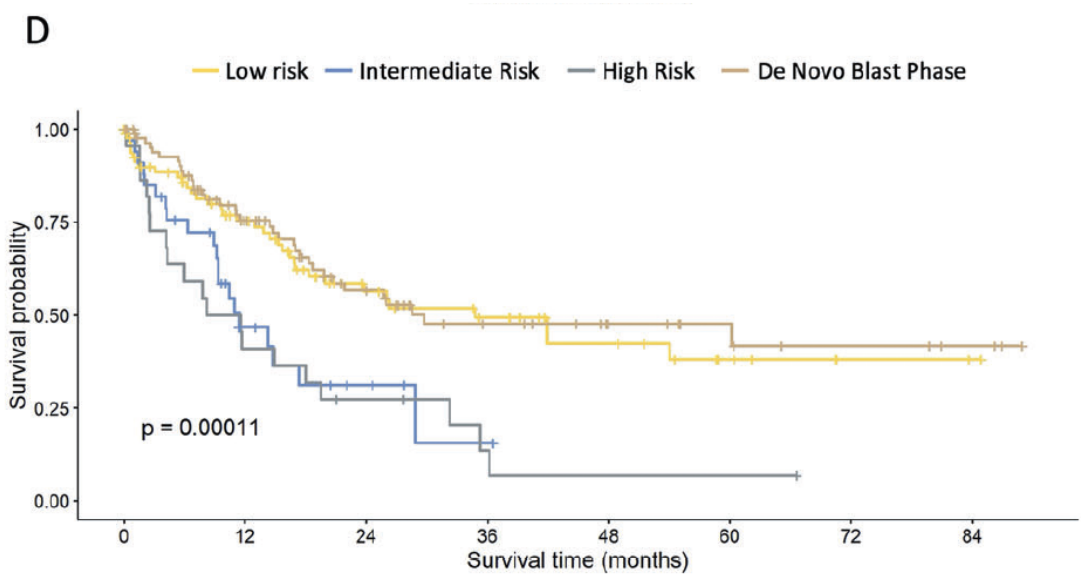
Annamaria Brioli[1,2,3]✉, Elza Lomaia[4], Christian Fabisch[2], Tomasz Sacha[5], Hana Klamova[6], Elena Morozova[7], Aleksandra Golos[8], Philipp Ernst[2], Ulla Olsson-Stromberg[9], Daniela Zackova[10], Franck E. Nicolini[11], Han Bao[12], Fausto Castagnetti[13,14], Elzbieta Patkowska[15], Jiri Mayer[10], Klaus Hirschbühl[16], Helena Podgornik[17,18], Edyta Paczkowska[19], Anne Parry[20], Thomas Ernst[2], Astghik Voskanyan[21], Elzbieta Szczepanek[22], Susanne Saussele[23], Georg-Nikolaus Franke[24], Alexander Kiani[25], Edgar Faber[26], Stefan Krause[27], Luis Felipe Casado[28], Krzysztof Lewandowski[29], Matthias Eder[3], Peter Anhut[30], Justyna Gil[31], Thomas Südhoff[32], Holger Hebart[33], Sonja Heibl[34], Markus Pfirrmann[12], Andreas Hochhaus[2] and Michael Lauseker[12]✉

Leukemia 2024

Table 4. Comparison between CML-BP as evolution of a chronic phase (secondary BP) and de novo CML-BP.

Variable		Secondary CML-BP (*N* = 151)	De novo CML-BP (*N* = 89)
Patient-related			
Sex, male, *n* (%)		97 (64.2%)	47 (52.8%)
Age at onset of CML-BP (yrs), median (range)		49 (18–85)	48 (20–86)
CML-related			
Morphology of CML-BP, n/N (%)	Myeloid	75/148 (50.7%)	42/85 (49.4%)
	Lymphoid	46/148 (31.1%)	25/85 (29.4%)
	Mixed	5/148 (3.4%)	5/85 (5.9%)
	Megakaryoblastic	1/148 (0.7%)	2/85 (2.4%)
	Unknown	21/148 (14.2%)	11/85 (12.9%)
	Not reported	3 (2.0%)	4 (4.5%)
Additional chromosomal abnormalities (ACAs), yes, n/N(%)	Complex karyotype	38/101 (37.6%)	14/73 (19.2%)
	Chr. 3q26.2 rearrangements	6/101 (5.9%)	3/73 (4.1%)
	−7/−7q	12/101 (11.9%)	0/73 (0%)
	+8	23/101 (22.8%)	0/73 (0%)
	others	41/101 (40.6%)	22/73 (30.1%)
	Not reported	50 (33.1%)	16 (18.0%)
High risk ACAs[a], yes, n/N(%)		56/101 (55.4%)	16/73 (21.9%)
	Not reported	50 (33.1%)	16 (18.0%)
Mutations in *BCR::ABL1*, yes, n/N(%)		39/104 (37.5%)	7/62 (11.3%)
	Not reported	47 (31.1%)	27 (30.3%)
CNS involvement, yes, n/N(%)		10/133 (7.5%)	11/81 (13.6%)
	Not reported	18 (11.9%)	8 (9.0%)
Extramedullary disease, yes, n/N(%)		27/136 (19.9%)	16/84 (19.0%)
	Not reported	15 (9.9%)	5 (5.6%)

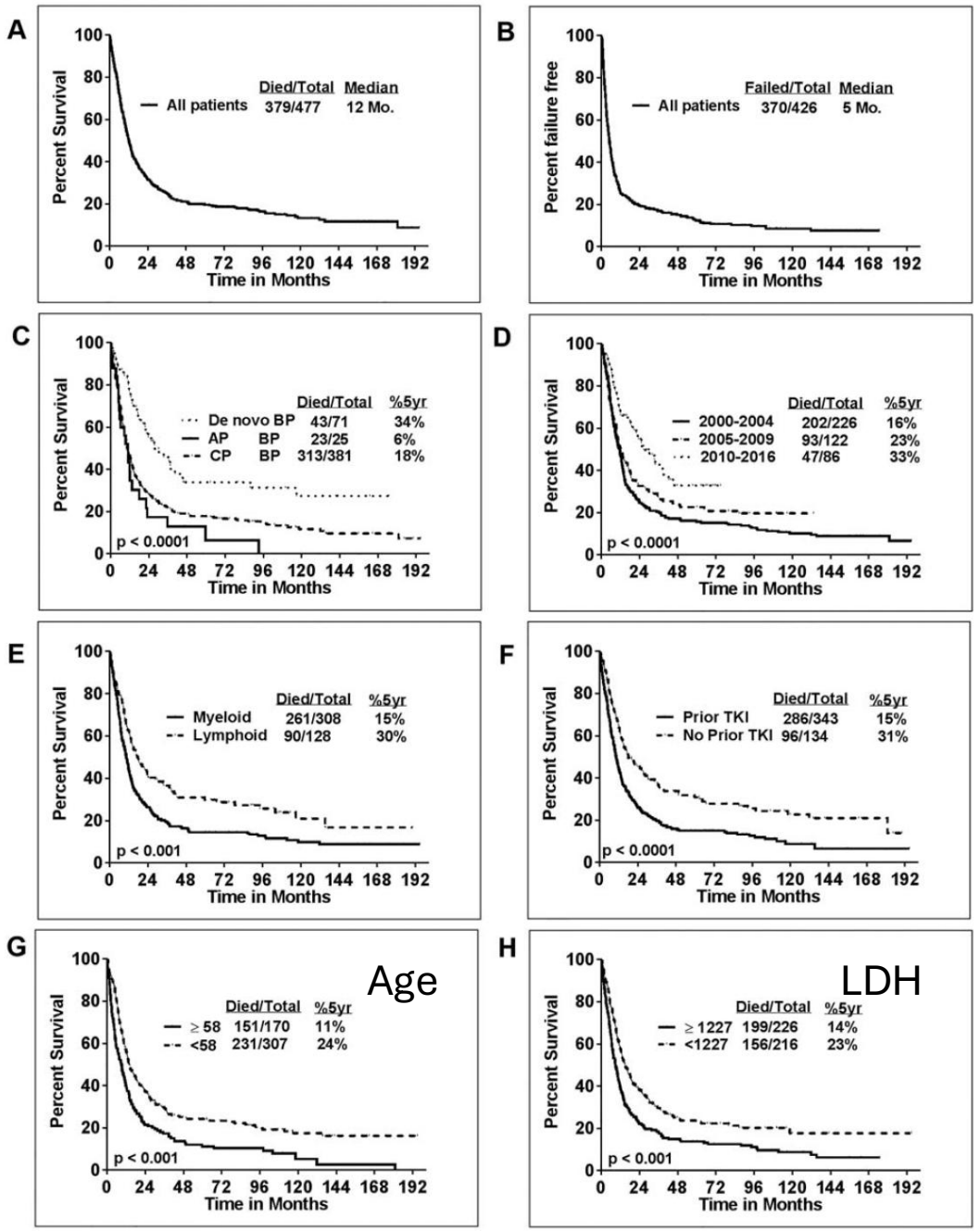
CML-BP chronic myeloid leukemia blast phase, *M* male, *F* female, *yrs* years, *chr.* chromosome, *CNS* central nervous system.
[a]High risk ACAs: +8, +Ph, i[17q], +17, +19, +21, 11q23 and 3q26.2 rearrangements, −7/7q abnormalities, complex karyotype.



brioli.annamaria@mh-hannover.de

N=477 patients with CML-BP (defined as 30% or EMD) From 1997 to 2016)

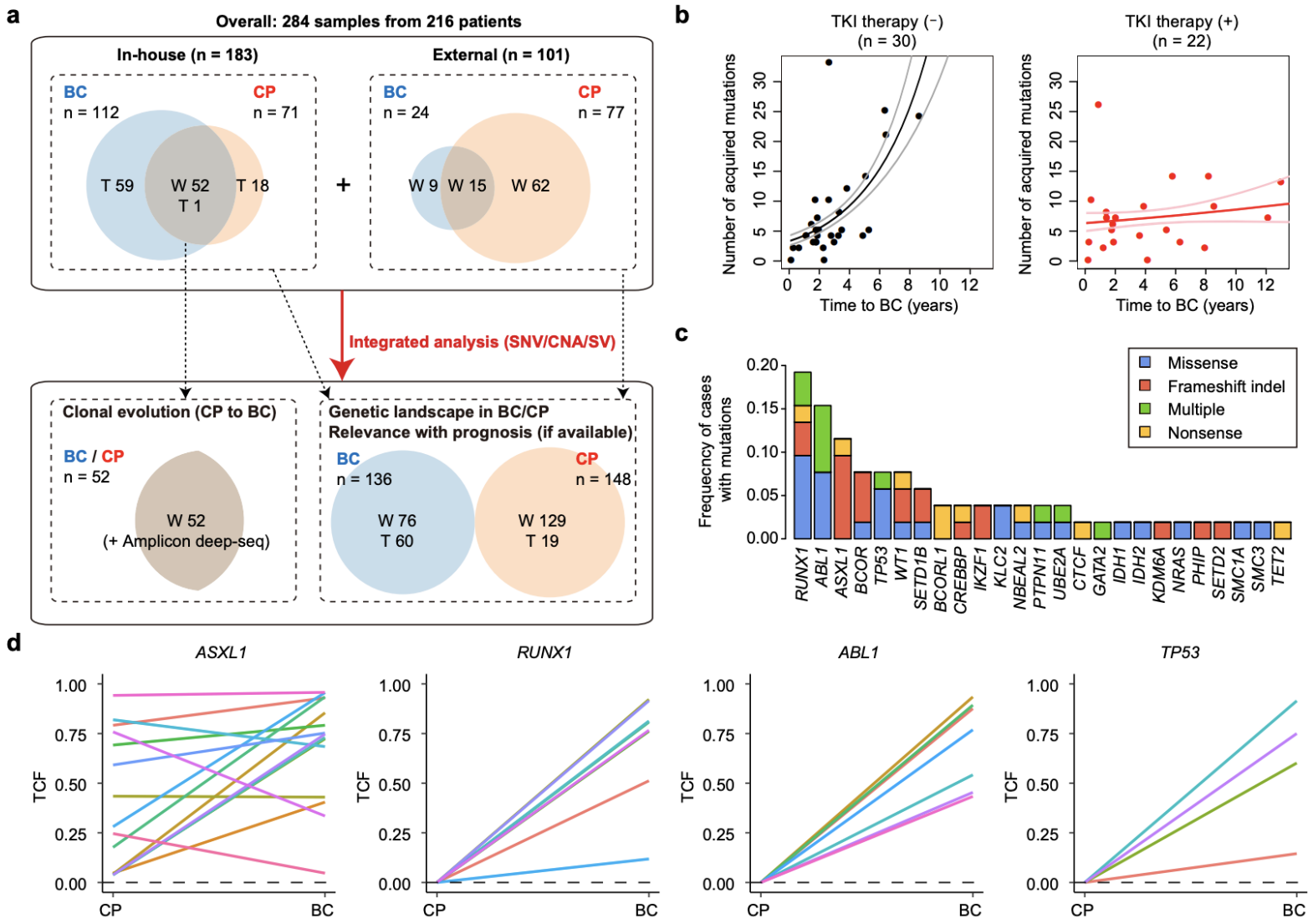
Prognostic Factors for Blast Phase



Jain P et al. Cancer 2017

- The number of mutations acquired during progression correlated with the time to progression, and inversely correlated with exposure to TKI therapy during CP

- ASXL1-mutated CP clones may be preferentially selected and may evolve by acquiring other drivers during the clonal development to BC



Ochi Y et al. Nat Commun 2021

Independent risk factors predicting OS in patients treated with TKI-based therapy were

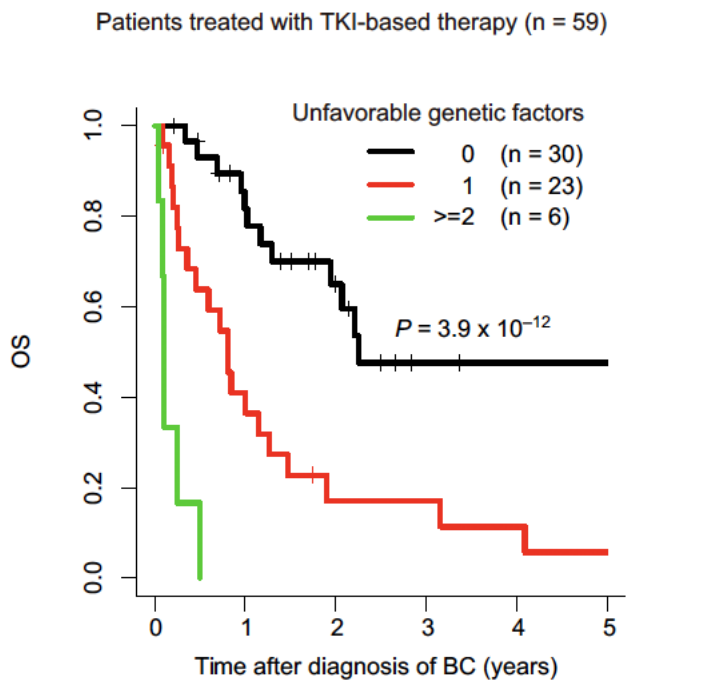
- ASXL1 mutations,
- complex CNAs,
- isochomosome (17q),
- trisomy 21.

b

Patients treated with TKI-based therapy (n = 59)

Variable	HR	95% CI	*P*
ASXL1 mutations	4.66	1.99-10.89	3.8×10^{-4} ***
Complex CNAs	4.44	2.13-9.27	7.0×10^{-5} ***
i(17q)	16.6	4.11-66.8	7.9×10^{-5} ***
+21	5.89	2.08-16.6	8.1×10^{-4} ***

c



Ochi Y et al. Nat Commun 2021

Therapeutic strategy: principles

- **Goal in AP**: regain chronic-phase rapidly and re-establish durable molecular control; consider consolidative **allogeneic HSCT** based on risk, response, and donor fitness.

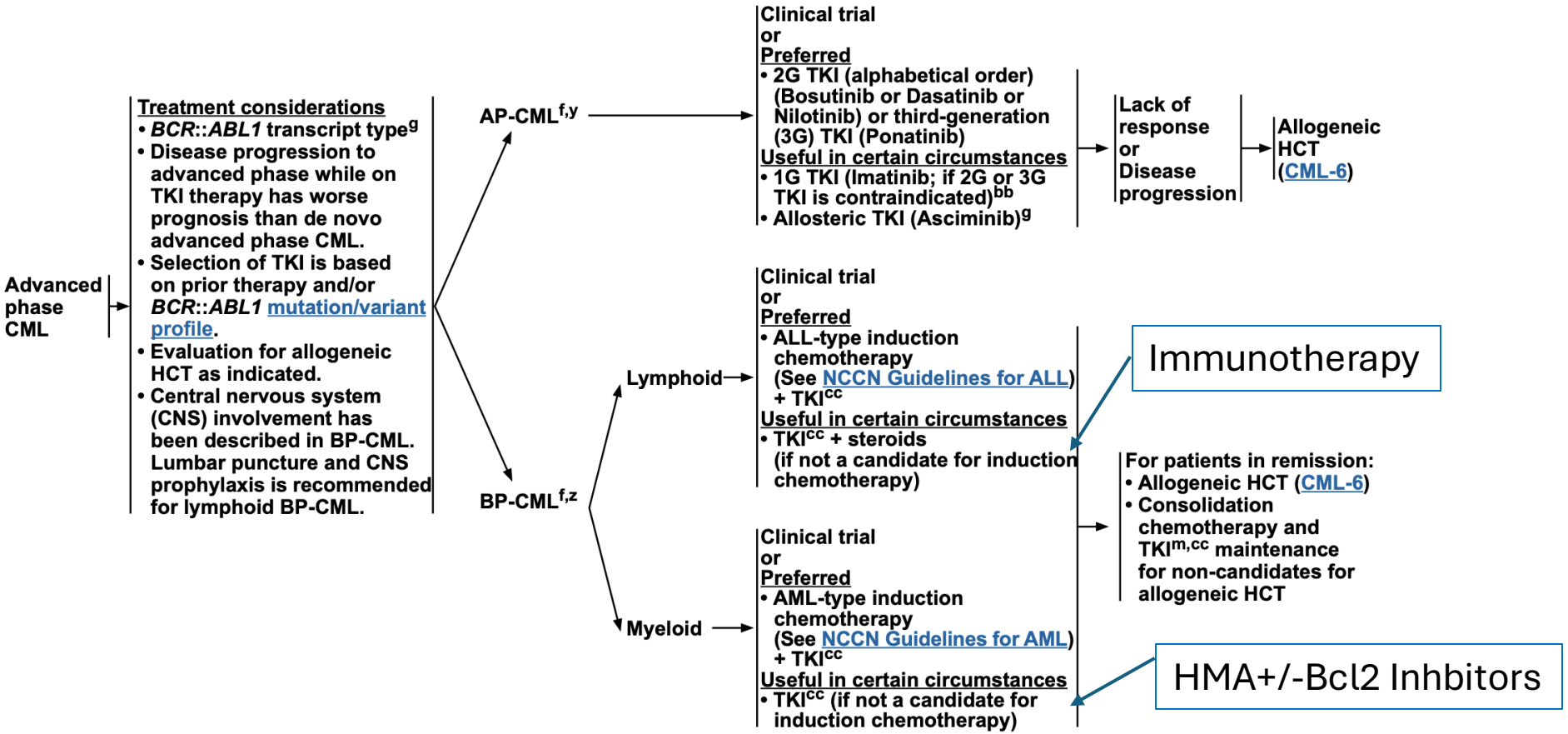
- **Goal in BP**: induce remission, then proceed to **HSCT** whenever feasible.

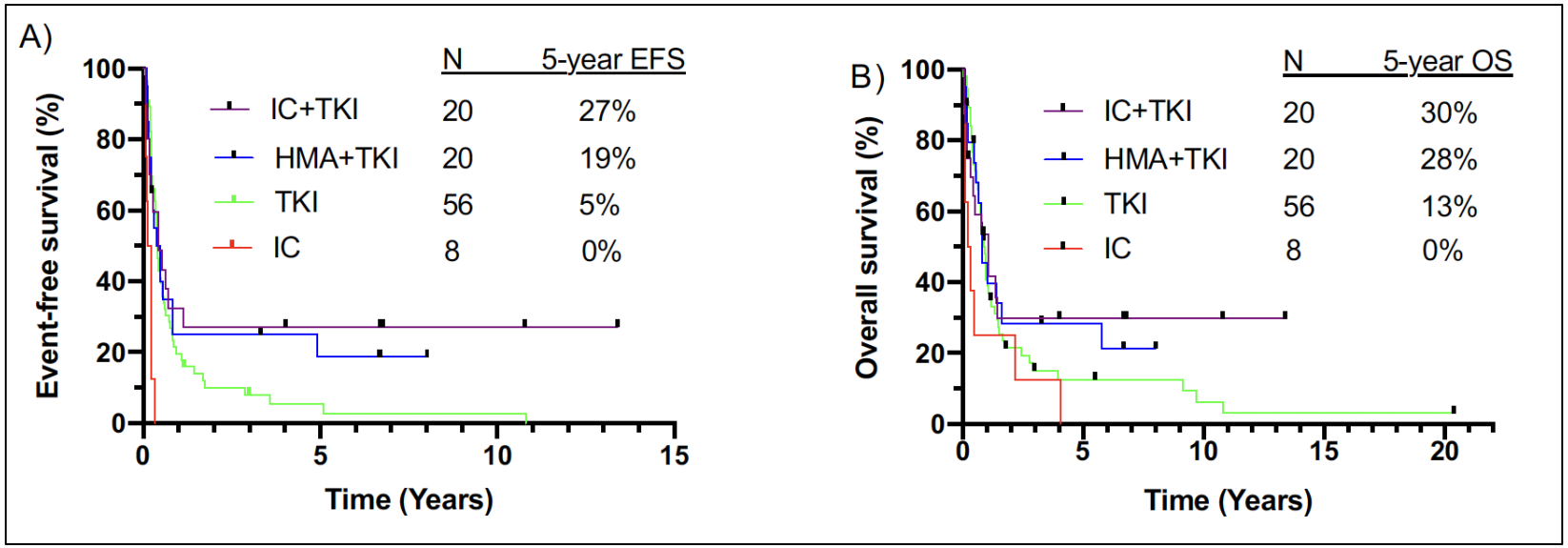
National Comprehensive Cancer Network®

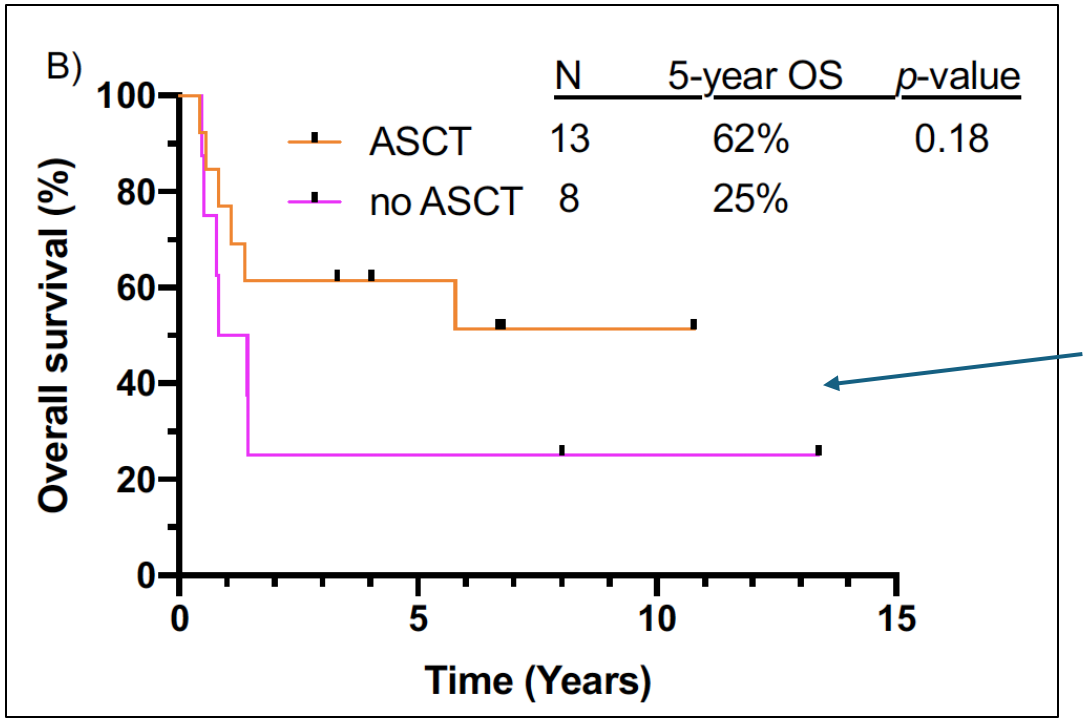
NCCN Guidelines Version 1.2026
Chronic Myeloid Leukemia

CLINICAL PRESENTATION

TREATMENT[i,l,m,aa]

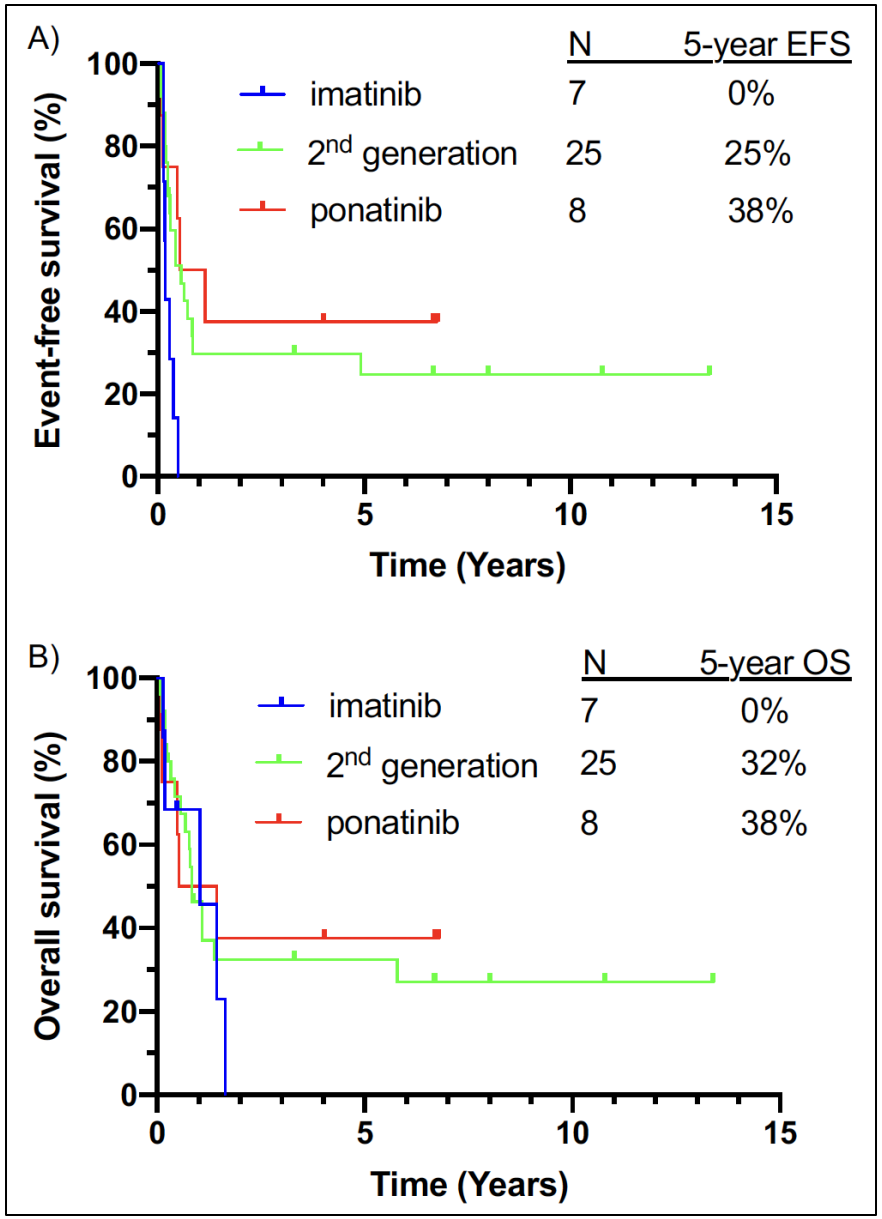






104 patients with CML-MBP from 2000 to 2019

Includes only patients who received combination therapy plus a TKI



Saxena et al. J Hematol Oncol 2021

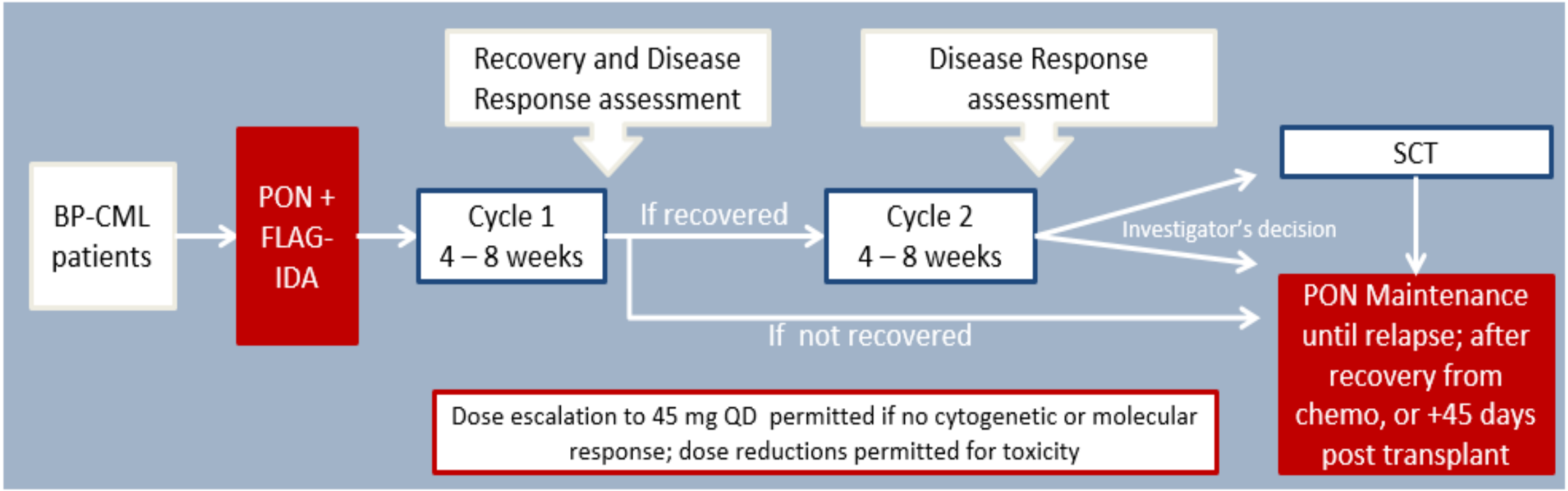
Resistance and BCR::ABL1 mutations

Table 5. Recommended tyrosine kinase inhibitors in case of *BCR::ABL1* mutations.

M244V	Nilotinib, dasatinib, bosutinib, ponatinib
Y253H	Dasatinib, bosutinib, ponatinib, asciminib
E255K/V	Dasatinib, ponatinib, asciminib
V299L	Nilotinib, ponatinib, asciminib
T315I	Ponatinib, asciminib
F317L/V/I/C, T315A	Nilotinib, bosutinib, ponatinib, asciminib
F359V/I/C	Dasatinib, ponatinib
A337V/T, L340Q, A344P, A433D, G463D/S, P465S/Q, V468F, F497L, I502L/N, V506L/M	Any ATP-competitive TKI

Apperley J. Leukemia (2025) 39:1797 – 1813

Treatment schedule
Salvage treatment, transplant consolidation



Primary outcome: Effective and tolerable dose of ponatinib

Secondary outcomes: Treatment response, safety, survival, transplant outcomes

Courtesy of Mhairi Copland

Copland et al, Lancet Haematol 2022; 9:e121-132

Response and survival

After cycle 1 (N=16)

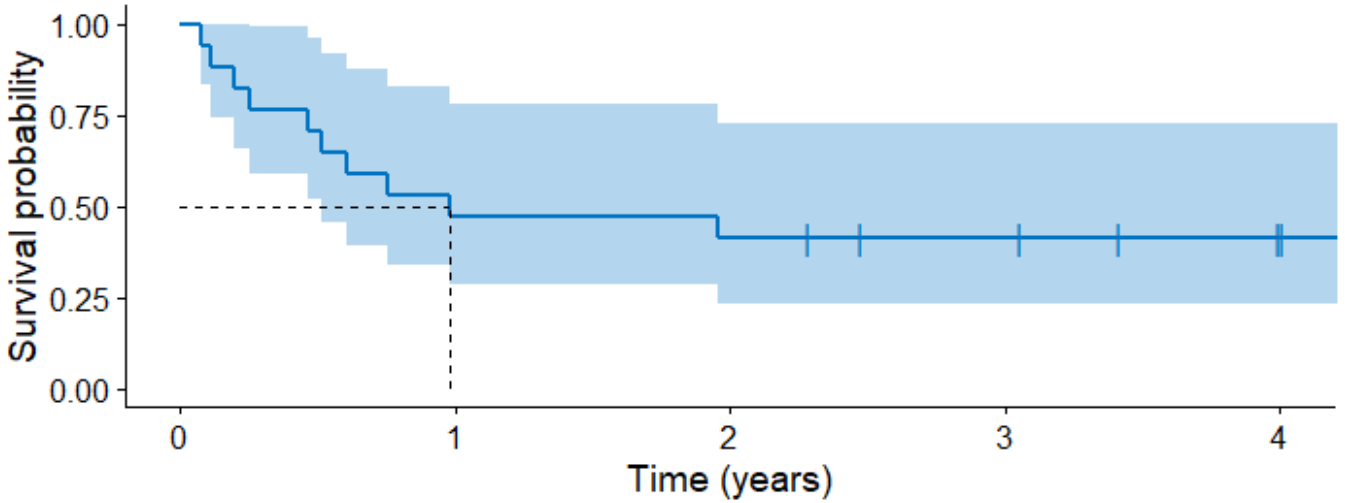
- Haematological 19% complete
- Chronic phase 69%
- Cytogenetic 50% complete
  13% partial
  6% minor
- Molecular 29% major

No additional patients achieved CCyR after cycle 2 (8/17 patients maintained CCyR).

All 5 patients achieving MMR after cycle 1 maintained this after cycle 2.

Median OS 12 months (6 to NR)

- 1-year 47% (28% to 78%)
- 3-year 41% (23% to 73%)



2 relapses occurred amongst 9 patients achieving CCyR.

Courtesy of Mhairi Copland

Copland et al, Lancet Haematol 2022; 9:e121-132

A Combination of Ponatinib and 5-Azacitidine in CML Advanced Phase or Myeloid Blast Crisis (**PONAZA**)

Setting	**Myeloid blast-phase CML (BP-CML)**
Induction regimen	**3 × 28-day cycles**: **ponatinib 45 mg once daily** + **azacitidine 75 mg/m^2 Days 1–7**
Post-induction ponatinib	**30 mg daily** for **HR**; **15 mg daily** for **MMR**
Azacitidine duration	Up to **24 months**
Number of patients (N)	**19**
Median age (range)	**63** years (**19–83**)
De novo BP / Progression	**10** de novo; **9** progressed
Responses	**CR** in **14** patients
Transplant	**7** proceeded to **alloSCT**
Follow-up / OS	At **31 months**, **median OS not reached**; **2-year OS 64.8%**
Favorable factors (trend)	**Blasts <30%** and **no major-route ACAs**
Cardiovascular AEs (CVAEs)	**4** total: **2** hypertension, **1** atrial fibrillation, **1** QTc prolongation

Rousselot P et al. EHA 2024

Phase 2 trial of **decitabine + venetoclax + ponatinib** in advanced-phase Ph+ myeloid disease

Population	20 patients total: 14 CML-blast phase, 4 CML-accelerated phase, 2 Ph+ AML
Follow-up	Median: 21.2 months (IQR 14.1–24.2)
Prior Therapy	60% (12 pts) had ≥2 prior BCR::ABL1 TKIs
Primary Endpoint (CR/CRi)	**50% (10/20)** patients achieved CR or CRi (CR in 1 [5%], CRi in 9 [45%])
Adverse Events (Grade 3–4, most common)	Febrile neutropenia: 40% (8 pts); Infection: 30% (6 pts); AST/ALT elevation: 25% (5 pts)
Cardiovascular Events	40% (8 pts) had ≥1 event (any grade)

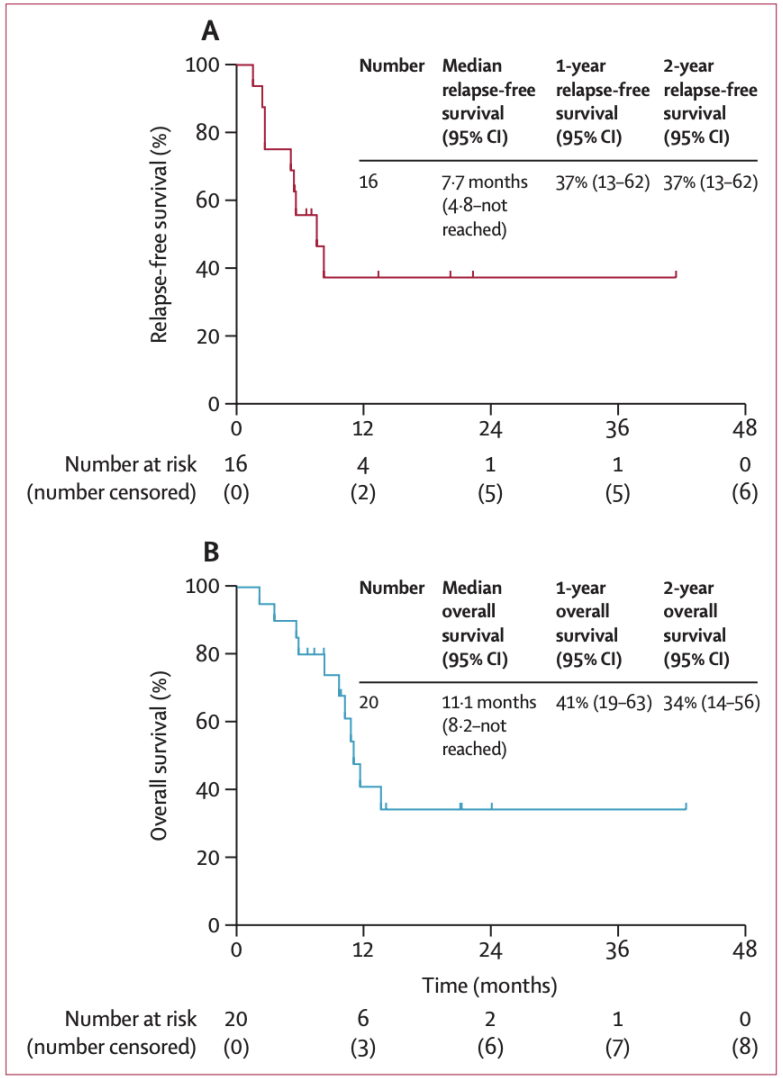
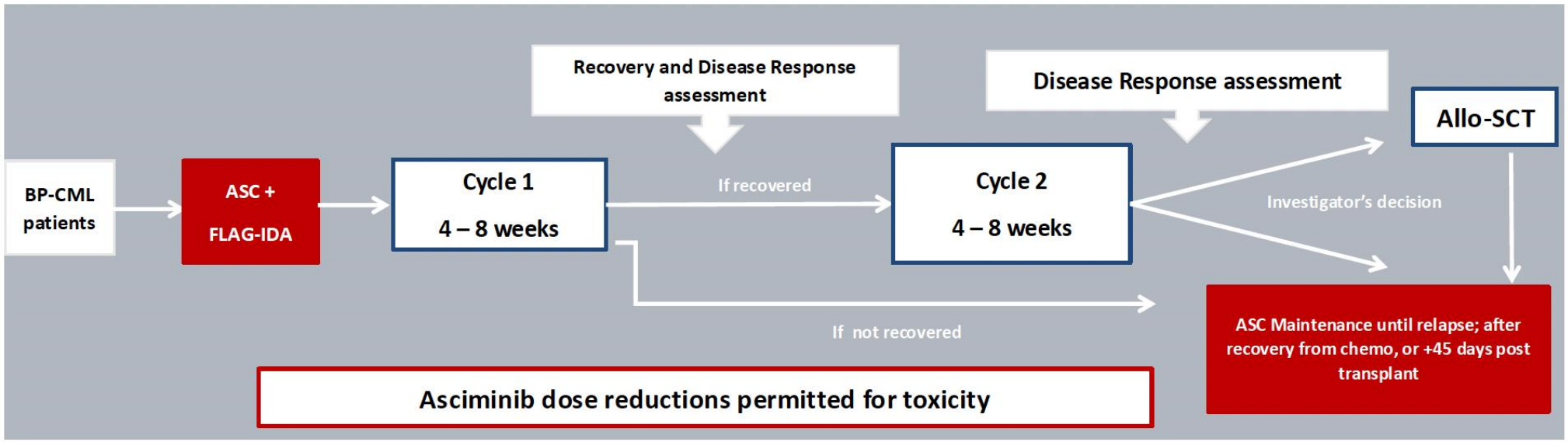


Figure 2: **Survival outcomes, (A) relapse-free survival and (B) overall survival**

Short NJ et al. Lancet Haematol 2024

NCT Number	Title	Recruiting?	Lead sponsor / Promoting center
NCT05376852	Decitabine and HQP1351 (**Olverembatinib**)-Based Chemotherapy for Advanced CML (Blast or Accelerated Phase)	**Unknown**	**Nanfang Hospital, Southern Medical University**
NCT06401603	Phase I Study of Decitabine**, Lisaftoclax**, and Olverembatinib in Advanced CML and Ph+ AML	**Yes**	**MD Anderson Cancer Center**
NCT03263572	Blinatumomab, Methotrexate, Cytarabine, and Ponatinib for Ph+ ALL / CML Lymphoid Blast Phase	**Yes**	**MD Anderson Cancer Center**
NCT03595917	ABL001 (**Asciminib**) + Dasatinib + Prednisone + Blinatumomab in BCR-ABL1+ Leukemias (includes CML lymphoid BP)	**Yes**	**Marlise Luskin, MD (Investigator-sponsor, Dana-Farber Cancer Institute)**
NCT04260022	Study of HQP1351 (Olverembatinib) in Refractory CML and Ph+ ALL (includes combination cohort with blinatumomab)	**Yes**	**Ascentage Pharma Group Inc.**

ABLATE
Asciminib in BLAsT phasE CML



CML- BC definition : WHO 2022

Primary outcome: tolerability of asciminib (of up to 200mg bd) in combination with Flag-Ida chemotherapy
Secondary outcomes: Treatment response, survival, transplant outcomes

Courtesy of Dragana Milojkovic

Most recognized prognostic factors for transplant outcome in advanced phase CML

Factor	Impact on Outcome	Citations
Disease phase at transplant	Strongest predictor; BP worst	(Khoury et al., 2011; Niederwieser et al., 2021; Thomas et al., 1986; Morozova et al., 2020)
Patient/donor age	Older age = worse survival	(Niederwieser et al., 2021; Thomas et al., 1986; Gratwohl, 2003)
Graft CD34+ cell dose	Higher dose = better survival	(Niederwieser et al., 2021)
Donor type/HLA match	Unrelated/mismatched = worse	(Khoury et al., 2011; Niederwieser et al., 2021; Gratwohl, 2003)
Pre-transplant response	Molecular/cytogenetic = better	(De Oliveira Medeiros et al., 2024)
BCR-ABL1 T315I mutation	Negative prognostic factor	(Tomuleasa et al., 2015)

Take home messages

Confirm phase

- The use of ICC or WHO criteria for the diagnosis of AP-CML and BP-CML is not recommended by ELN2025 and NCCN, however these classifications open our minds on the disease

Diagnosis

- **NGS** for BCR::ABL1 kinase mutations and other somatic myeloid and lymphoid alterations (+ Ig for LBC)

AP management

- Intensify to mutation-tailored 2G TKI or ponatinib
- Proceed to HSCT if poor molecular control

BP management

- **de novo LBP is a multilineage Ph+ ALL?**
- **MBP**: go for **HSCT** whenever possible

Post-remission/HSCT

MRD-directed **TKI maintenance**; frequent molecular monitoring.

1ST INTERNATIONAL CONFERENCE ON

Ph+Leukemias

Bologna, Royal Hotel Carlton **September 29-30, 2025**

Thank you!