CML in Blastcrisis

Philipp le Coutre, Charité

Disclosures:

- Novartis, BMS, Pfizer, Incyte, Blueprint, GSK, JAZZ

Charité

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1845

R. Virchow

Berlin

Weißes Blut.

Außer sehr wenig rothen Blutkörperchen bestand der ungleich größere Theil aus denselben farblosen oder weißen Körpern, die auch im normalen Blut vorkommen, nämlich kleinen, nicht ganz regelmäßigen Protoinmoleeülen, größeren, körnigen, fetthaltigen, kernlosen Körperchen und granulirten Zellen mit einem rundlichen, hufeisenförmigen oder kleeblattartigen oder mit mehreren napfförmigen, distincten Kernen. Die größeren dieser Zellen hatten ein leicht gelbliches Aussehen. Das Verhältniß zwischen den farbigen und farblosen Blutkörperchen stellte sich hier ungefähr umgekehrt, wie im normalen Blut, indem die farblosen die Regel, die farbigen eine Art von Ausnahme zu bilden schienen. Wenn ich daher von weißem Blute spreche, so meine ich in der That ein Blut, in welchem die Proportion zwischen den rothen und farblosen (in Masse weißen) Blutkörperchen eine umgekehrte ist, ohne daß eine Beimischung fremdartiger chemischer oder morphologischer Elemente zu bemerken wäre.

ich würde mich glücklich schätzen, der Wissenschaft dadurch zu einer neuen und, wie es mir scheint, nicht unwichtigen Thatsache verholfen zu haben. —

Dr. Virchow.

LEUCOCYTHEMIA,

or

WHITE CELL BLOOD,

IN RELATION TO THE

PHYSIOLOGY AND PATHOLOGY OF THE LYMPHATIC GLANDULAR SYSTEM.

BY JOHN HUGHES BENNETT, M.D., F.R.S.E.,

PROFESSOR OF INSTITUTES OF MEDICINE AND OF CLINICAL MEDICINE IN THE UNIVERSITY, AND PRESIDENT OF THE PHYSIOLOGICAL SOCIETY, EDINBURGH. MEMBER OF THE AMERICAN PHILOSOPHICAL SOCIETY; OF THE IMPERIAL SOCIETY OF PHYSICIANS OF VIENNA; OF THE MEDICAL ASSOCIATION OF PRUSSIA; OF THE ANATOMICAL AND BIOLOGICAL SOCIETIES OF PARIS; OF THE MEDICAL SOCIETIES OF SWEDEN, COPENHAGEN, ETC. ETC.

WITH TWO COLOURED LITHOGRAPHS, AND NUMEROUS WOODCUTS.

EDINBURGH: SUTHERLAND AND KNOX.
LONDON: SIMPKIN, MARSHALL, & CO.

MDCCCLII.

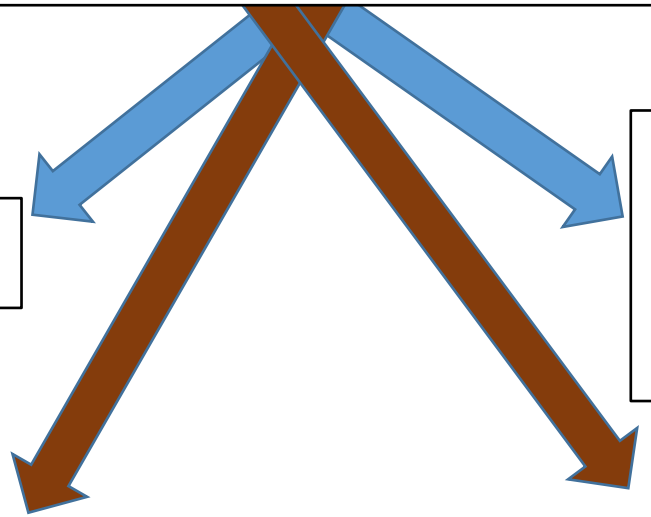
J. Bennett

Edinburgh

CG Geary, British Journal of Haematology, 2000

CML blast crisis: definitions

Blast crisis:
> 20 % blast cells in peripheral blood or bone marrow or extramedullary manifestation of CML



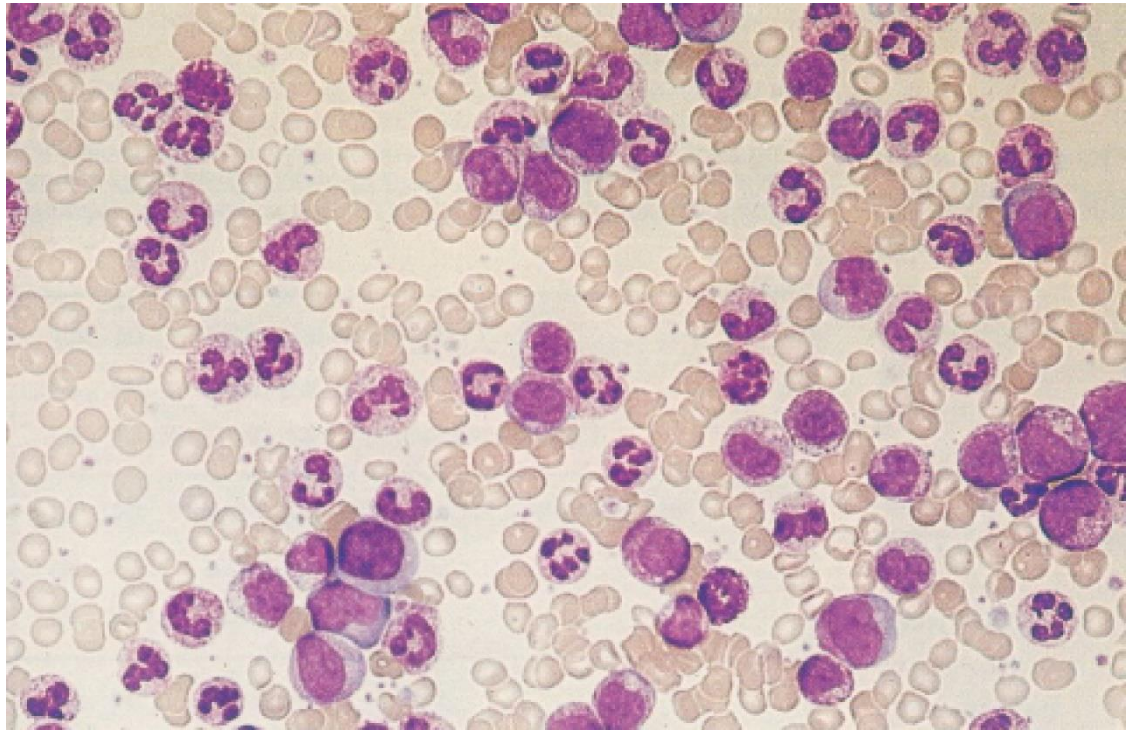
De novo blast crisis

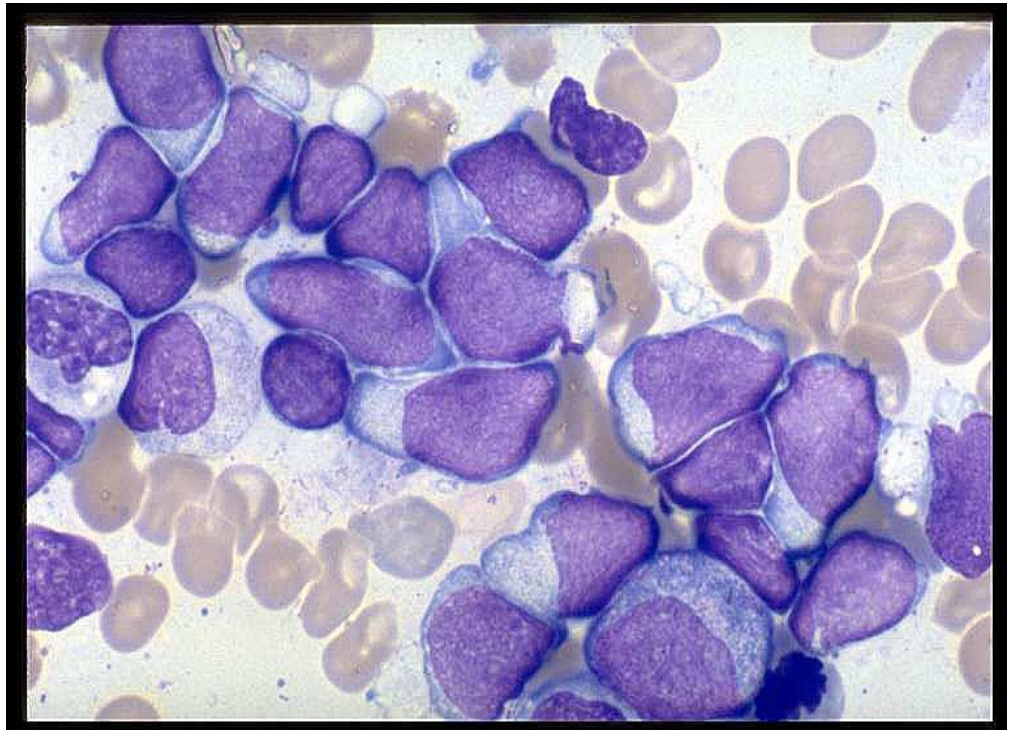
Secondary blast brisis following chronic phase CML

Myeloid blast crisis

Lymphoid blast crisis

Chronic Phase versus Blast Crisis: Cytology





WHO Clasification 2022

Leukemia www.nature.com/leu

REVIEW ARTICLE OPEN

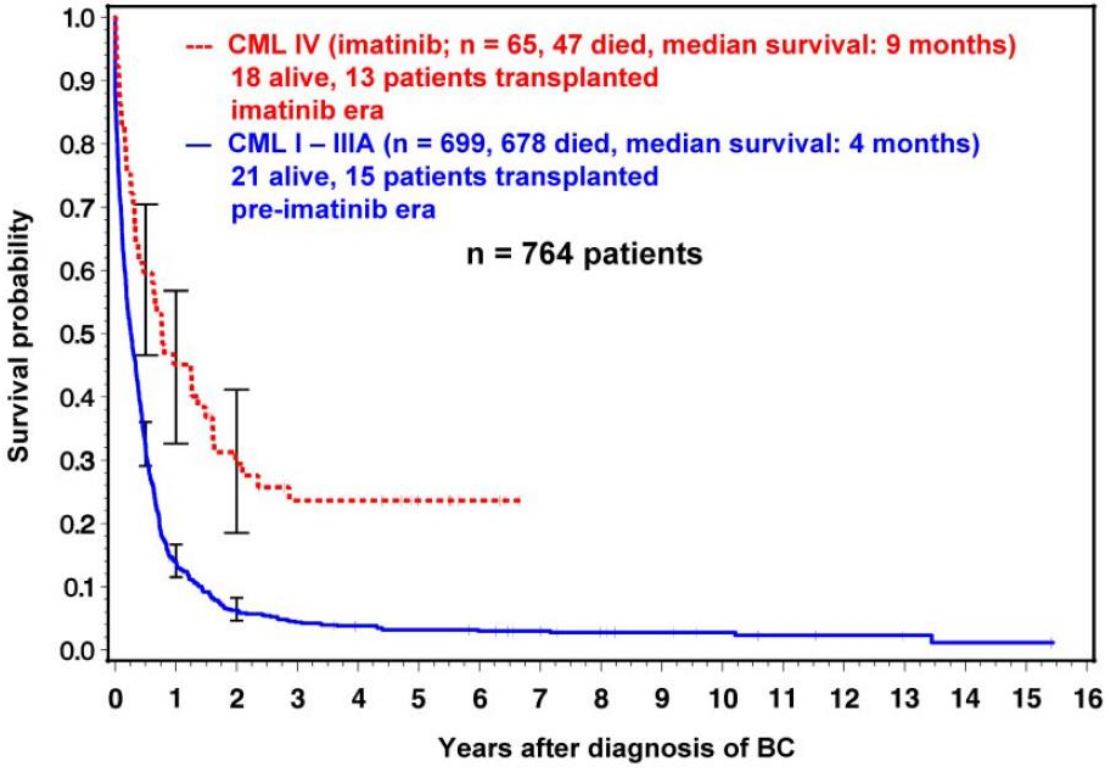
The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/ Dendritic Neoplasms

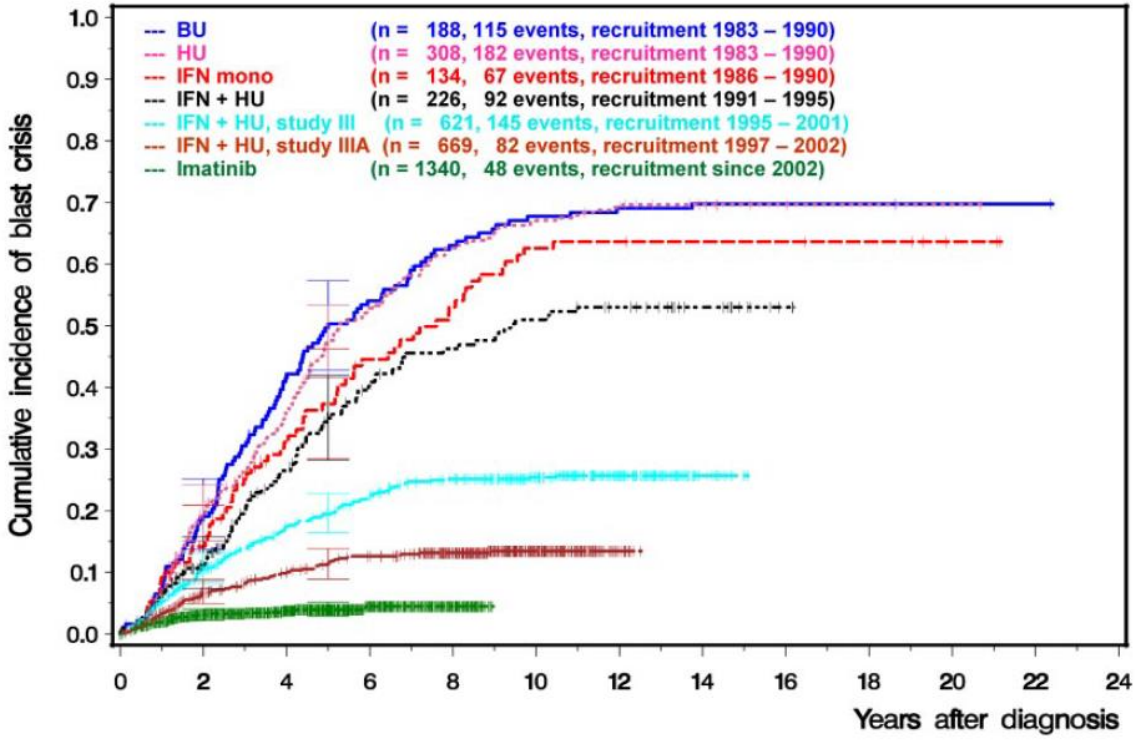
CML is 80–90% [10, 11]. The designation of AP has thus become less relevant, where resistance stemming from *ABL1* kinase mutations and/or additional cytogenetic abnormalities and the development of BP represent key disease attributes [12, 13]. Accordingly, AP is omitted in the current classification in favour of an emphasis on high risk features associated with CP progression and resistance to TKI. Criteria for BP include: (1) ≥20% myeloid blasts in the blood or bone marrow; or (2) the presence of an extramedullary proliferation of blasts; or (3) the presence of increased lymphoblasts in peripheral blood or bone marrow. The

Blast crisis: Additional clinical features

- Low platelets, thrombopenia
- Splenomegaly
- Additional chromosomal abnormalities
- Anemia
- Fever
- Chills
- Bleeding disorders
- Worstening of clinical performance status

Overall survival of blast crisis (historical data)





R Hehlmann Blood 2012

Response to tyrosine kinase inhibitors

TKI	Prior TKI (yes/no)	Reference(s)	No. of patients	CHR (%)	CCyR (%)	alloHSCT (%)	Median OS (mo)
Imatinib	No	37	mBP = 38 lBP = 20	10.5 20	7.9 10	4.5 N/A	N/A N/A
	No	40,41	229 (mBP)	15.3	7.4	5	6.9
	No	38	75	21.3	18.7	9.3	6.5
	No	42	30	33	0	N/A	OS 36% at 1 year
	No	39	92	26.1	9.8	9.8	7.0
Dasatinib	Yes	47	mBP = 23 lBP/Ph$^+$ALL = 10	34.8 70	26.1 30	N/A 10	N/A N/A
	Yes	43,46	mBP = 149 lBP = 61	17.4 18.0	17.5 36.8	6.0 9.8	7.7–7.9 9.0–11.4
Nilotinib	Yes	45	33	6.1	6.1	N/A	N/A
	Yes	44	mBP = 105 lBP = 31	24 21	30 32	11 6	10.1 7.9
	Yes	51	mBP = 133 lBP = 50	6.8 14.0	8.3 26.0	N/A N/A	OS 63% at 18 months for mBP/lBP
Bosutinib	Yes	49	Second line = 36 ≥Third line = 28	27 4	37 17	N/A N/A	11.2 8.9
Ponatinib	Yes	48,52	62 (incl. 24 with T315I)	21	17.4	9.7	OS 29% at 1 year & 9% at 3 years

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Response to TKI plus Chemo

Myeloid

Combination	Reference(s)	No. of patients	CHR (%)	CCyR (%)	alloHSCT (%)	Median OS (mo)
Ponatinib + FLAG-IDA	10	17 (incl. 4 lBP)	19	50	70.6	12
Dasatinib + FLAG-IDA	98	4 (incl 1 lBP)	100	75	100	N/A
Imatinib + '7+3' daunorubicin/cytarabine	99	36	56	30.6	30.6	16
Imatinib + idarubicin/idarubicin + cytarabine	100	19	47	15.8	26.3	5
Imatinib + mitoxantrone/etoposide	101	16	81	N/A	37.5	6.4
Imatinib + decitabine	53	10	20	10	N/A	3.5
Dasatinib + decitabine	54	30 (incl AP $n = 7$ and Ph^+AML $n = 4$)	48	33.3	26.7	13.8
Dasatinib or nilotinib or ponatinib + azacytidine	55	7	71	43	N/A	27.4
Imatinib + omacetaxine	102	12	58	27.3	72.7	N/A; 75% OS at 12 months

Lymphoid

Combination	Reference(s)	No. of patients	CHR (%)	CCyR (%)	alloHSCT (%)	Median OS (mo)
Imatinib + vincristine + dexamethasone	58	12	91.7	33.3	58.3	13
Imatinib or dasatinib + HyperCVAD	56	42	90.4	58	42.9	17

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Response after allo Transplantation

Dates of study	No. of patients	3-year OS (%)	3-year PFS (%)	Relapse incidence (%)	Non-relapse mortality (%)
2000–2009	63	36	23	40	33
1999–2004	80 (active BP-CML)	14	10	36	54
2004–2016	170	39	26	51	23
1990–2018	147 (incl. 51 AP-CML)	34	26	43	28

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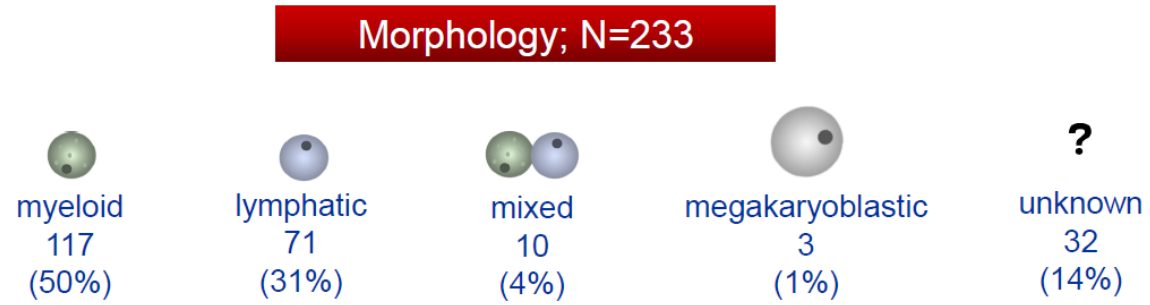
Patient Population

Variabel	N	
Gender, m/f, n (%)	240	144 (60.0%)/96 (40.0%)
Age at CML-Diagnosis (years), Median (range)	240	45 (13-86)
Age at CML-Blast crisis (years), Median (range)	240	49 (18-86)
Phase at diagnosis	240	
chronic phase, n(%)		151 (62.9%)
Blastencrisis, n(%)		89 (37.0%)
Diagnosis of BC after Diagnosis of CML (months), median (range)	151	29.1 (0.1-378)
ELTS-Score at diagnosis of CML (only in CP patients)	151	
low risk, n (%)		36 (39.6%)
intermediate risk, n(%)		33 (36.3%)
high risk, n(%)		22 (24.2%)



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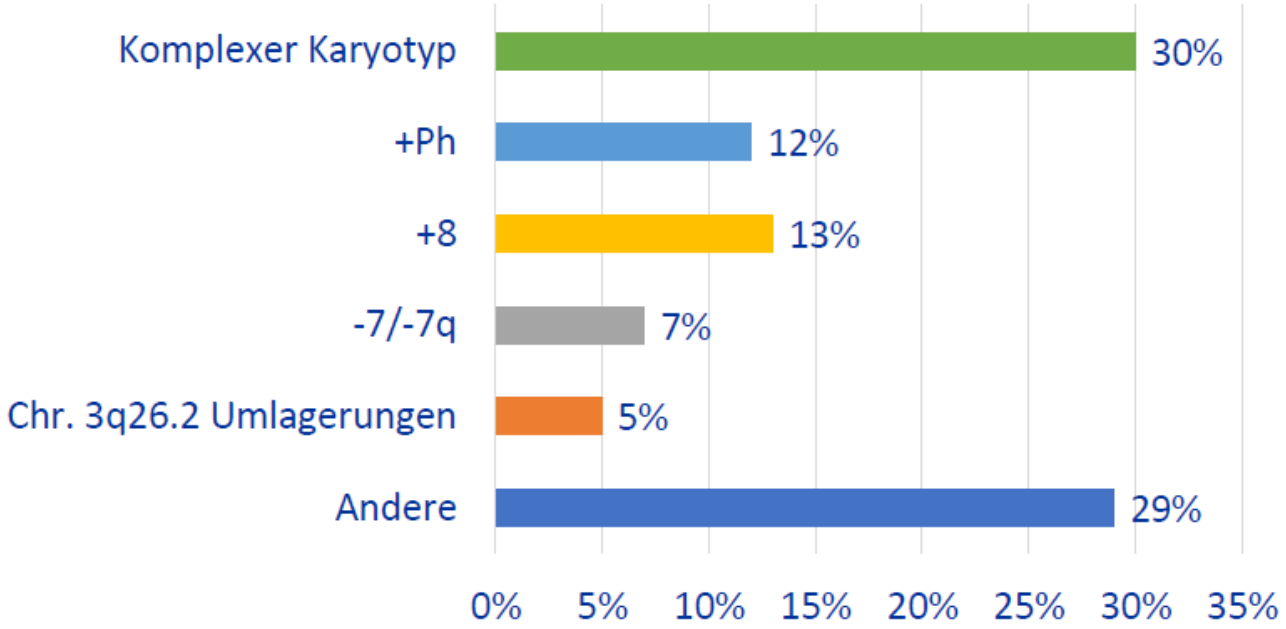
Blast Crisis Patients: Biology of Blast Crisis

Addtl. chromosomal abnormalities (ACAs)

ACAs in: 101/174 Pat. **(58%)**



High risk ACAs: 72/174 (41%)

BCR::ABL1 - Mutations and Highrisk characteristics

new mutations,
n/N (%): 46/166 (28%)

CNS-Involvement,
n/N (%): 21/214 (10%)

Extramedullary manifestations,
n/N (%): 43/220 (20%)

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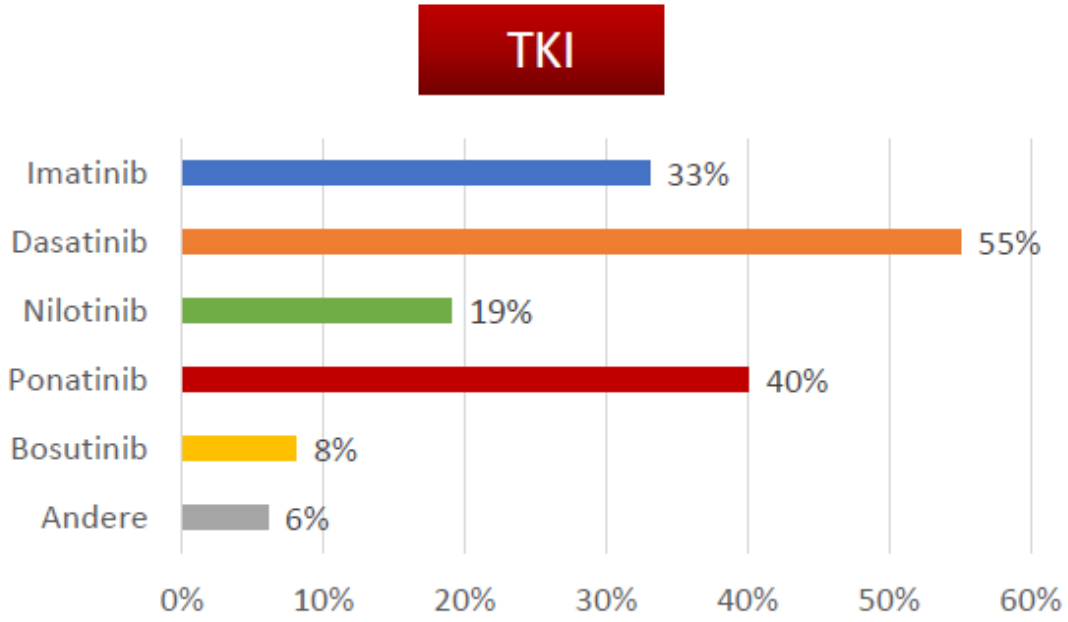
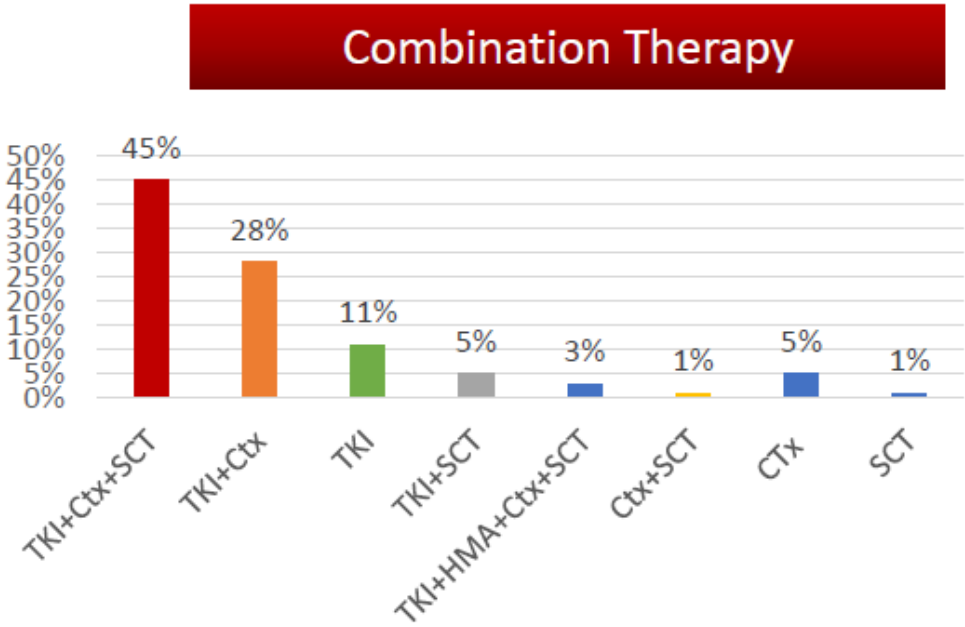
Treatment of Blast Crisis





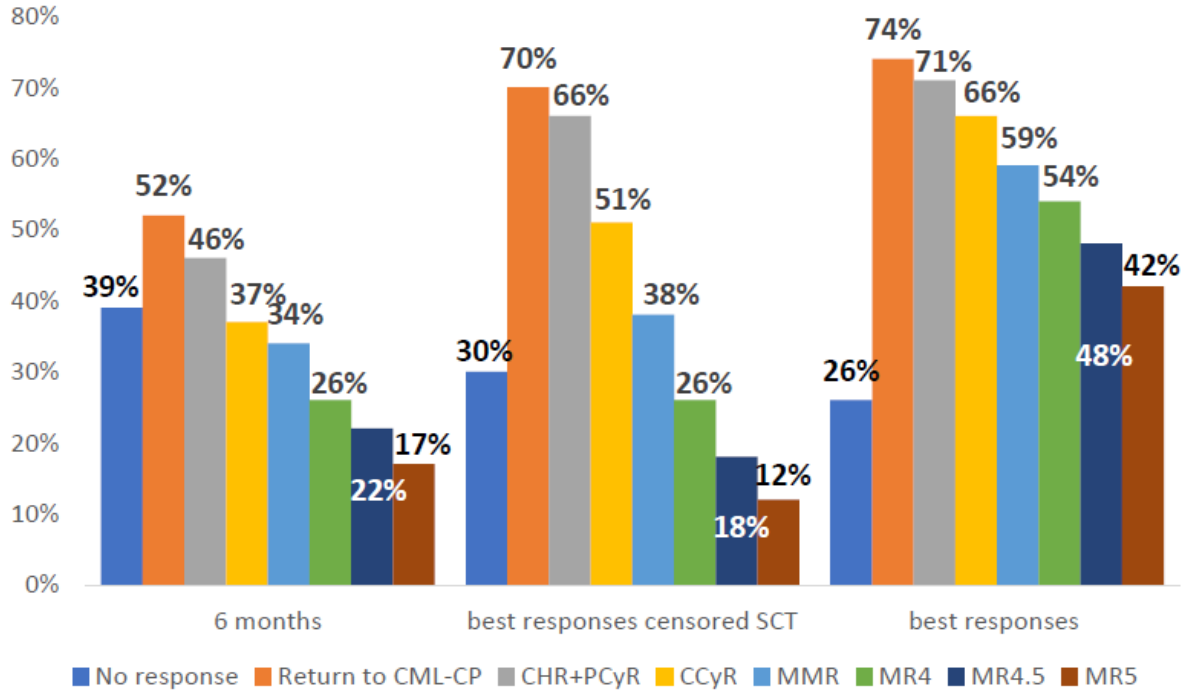
Median number of therapies: n = 3

55% received allo-TX

Courtesy of A Brioli, Greifswald, 2023

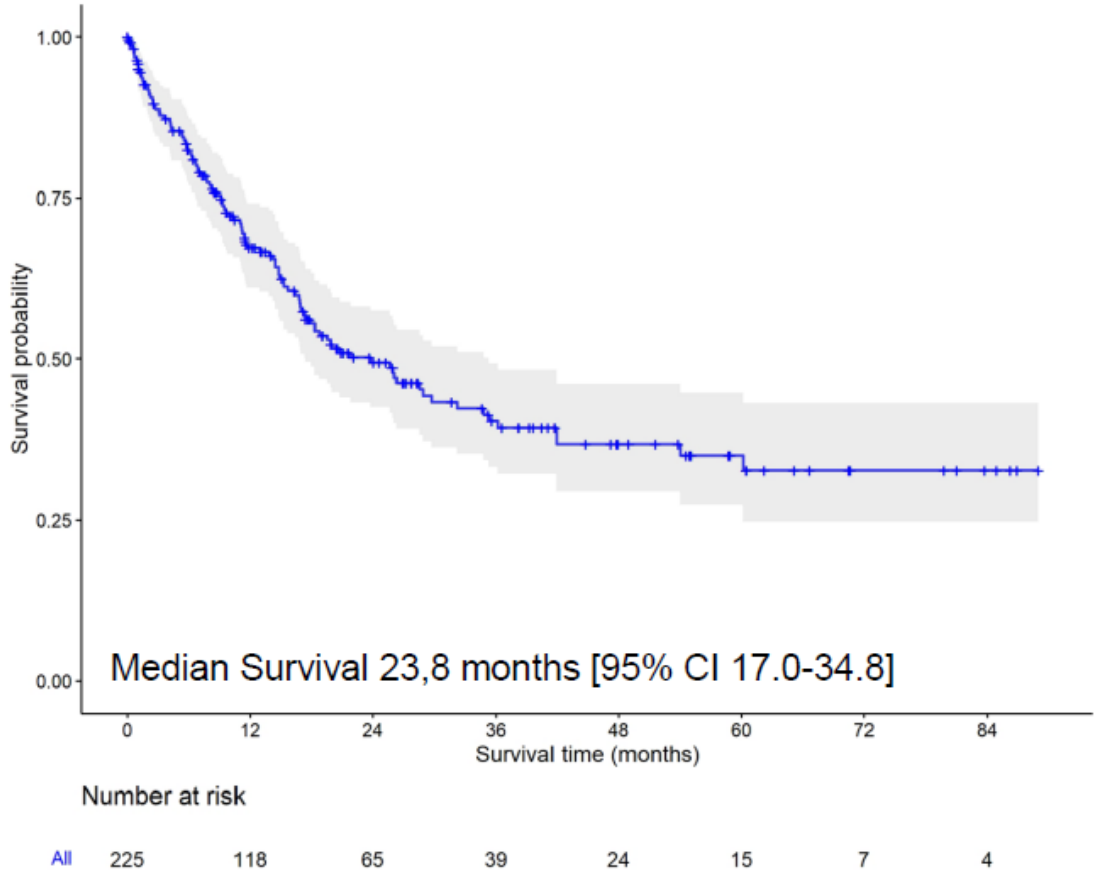
Response rates and Overall Survival

Responses



38/106 Pat. (36%) died within 6 months of diagnosis of blast crisis

Overall Survival



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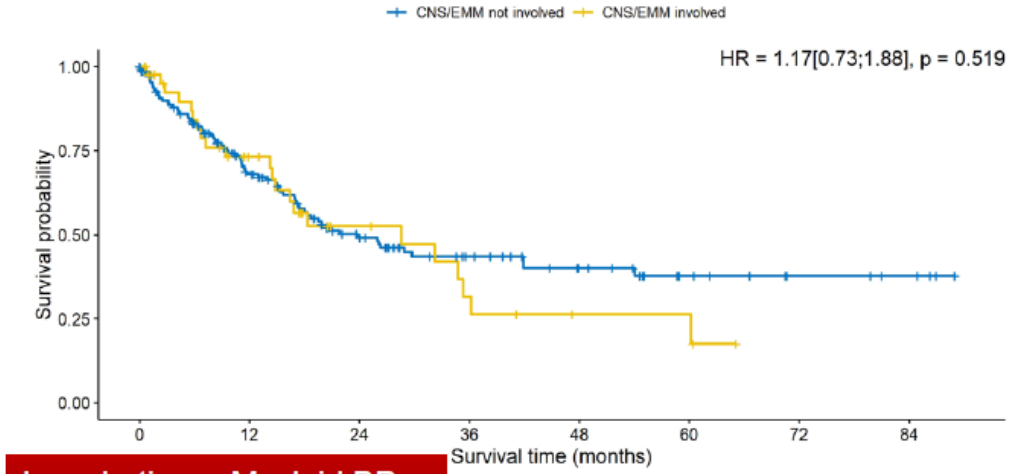
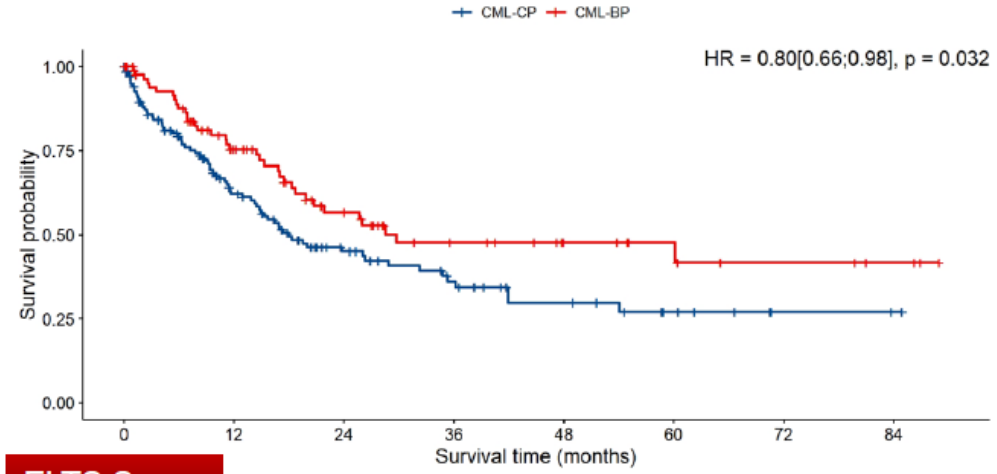
Overall survival by subgroup

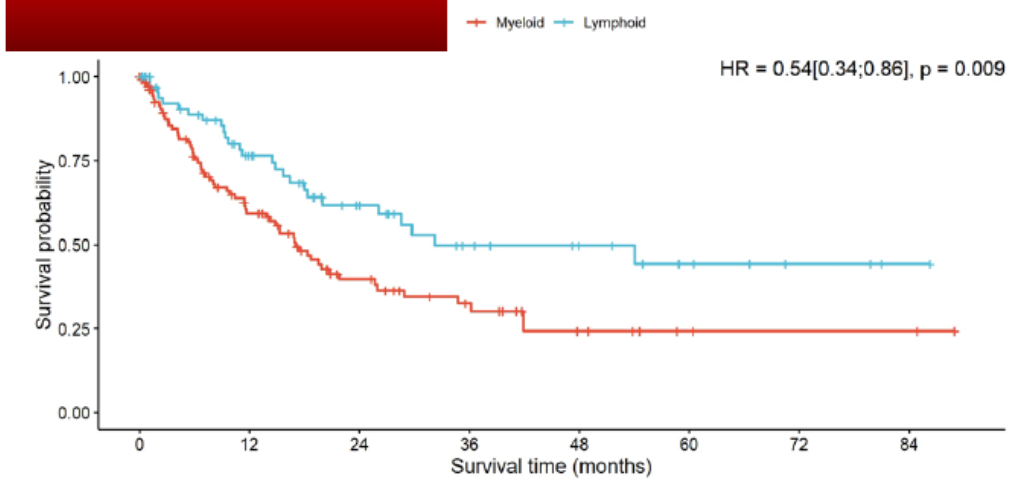
ZNS/EM-involvement vs all others



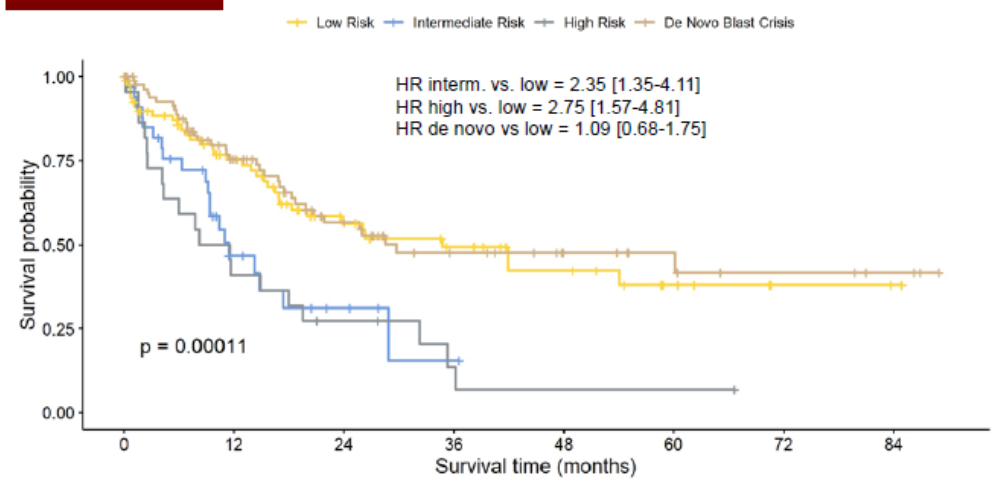
De novo vs secondary BP



Lymphatic vs. Myeloid BP



ELTS Score



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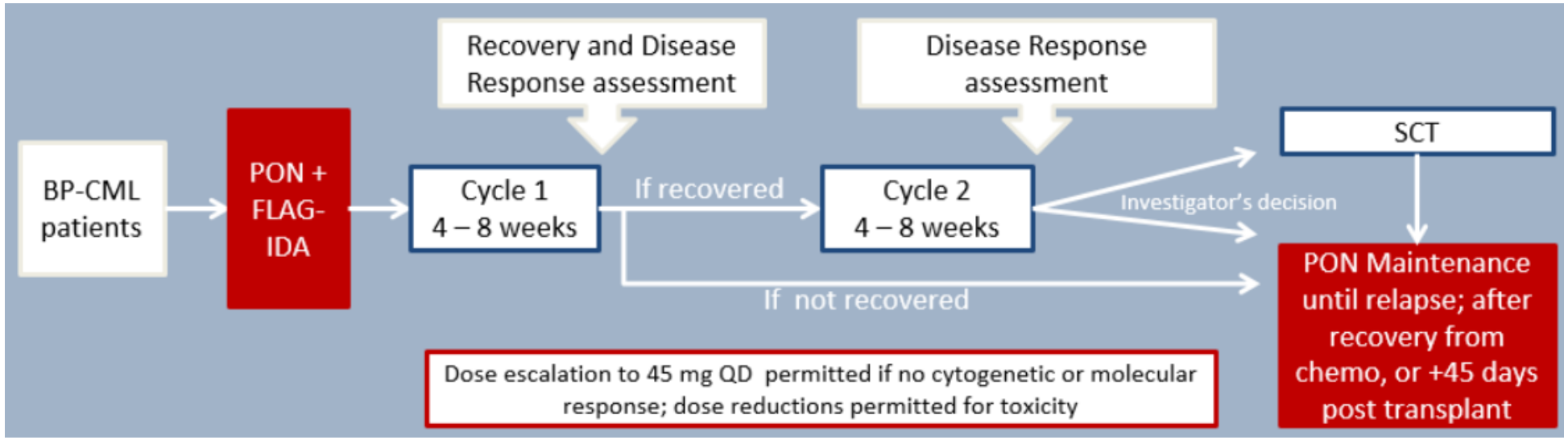
Blast crisis treatment

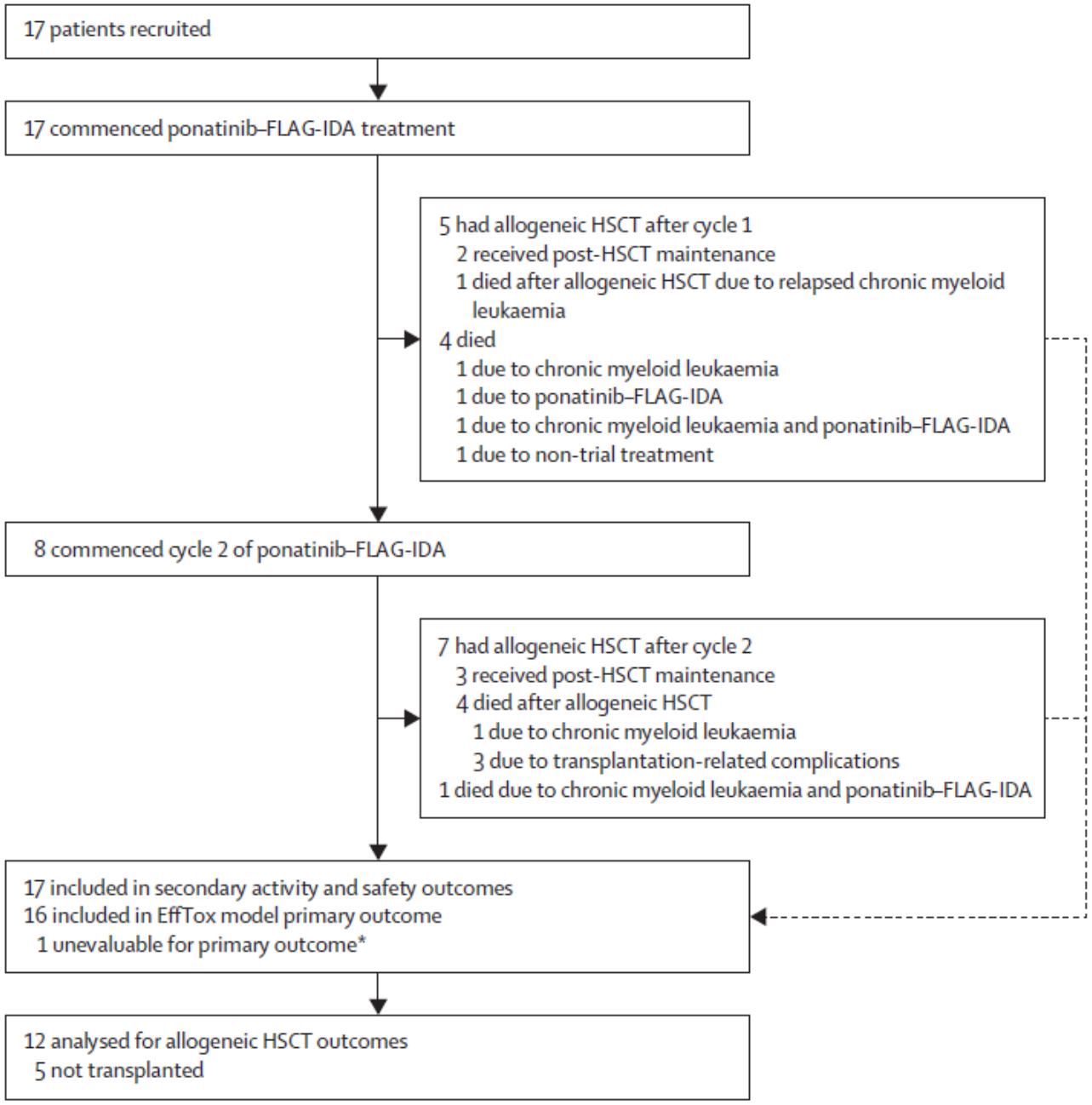


Variable	Level	Overall N (%)
Gender	Female Male	5 (29.4) 12 (70.6)
Age	Mean Range	36.41 (13.4) 16 – 64
Additional chromosomal abnormality	No Not Known Yes	6 (35.3) 3 (17.6) 8 (47.1)
Detectable Mutation	No Present Missing	12 (70.6) 3 (17.6) 2 (11.8)
Blast Phase Phenotype	Myeloid Lymphoid Bi-Phenotypic	9 (52.9) 4 (23.5) 4 (23.5)
Disease Status	De-Novo Progression	10 (58.8) 7 (41.2)

M Copland et al.: Lancet Hem 2021

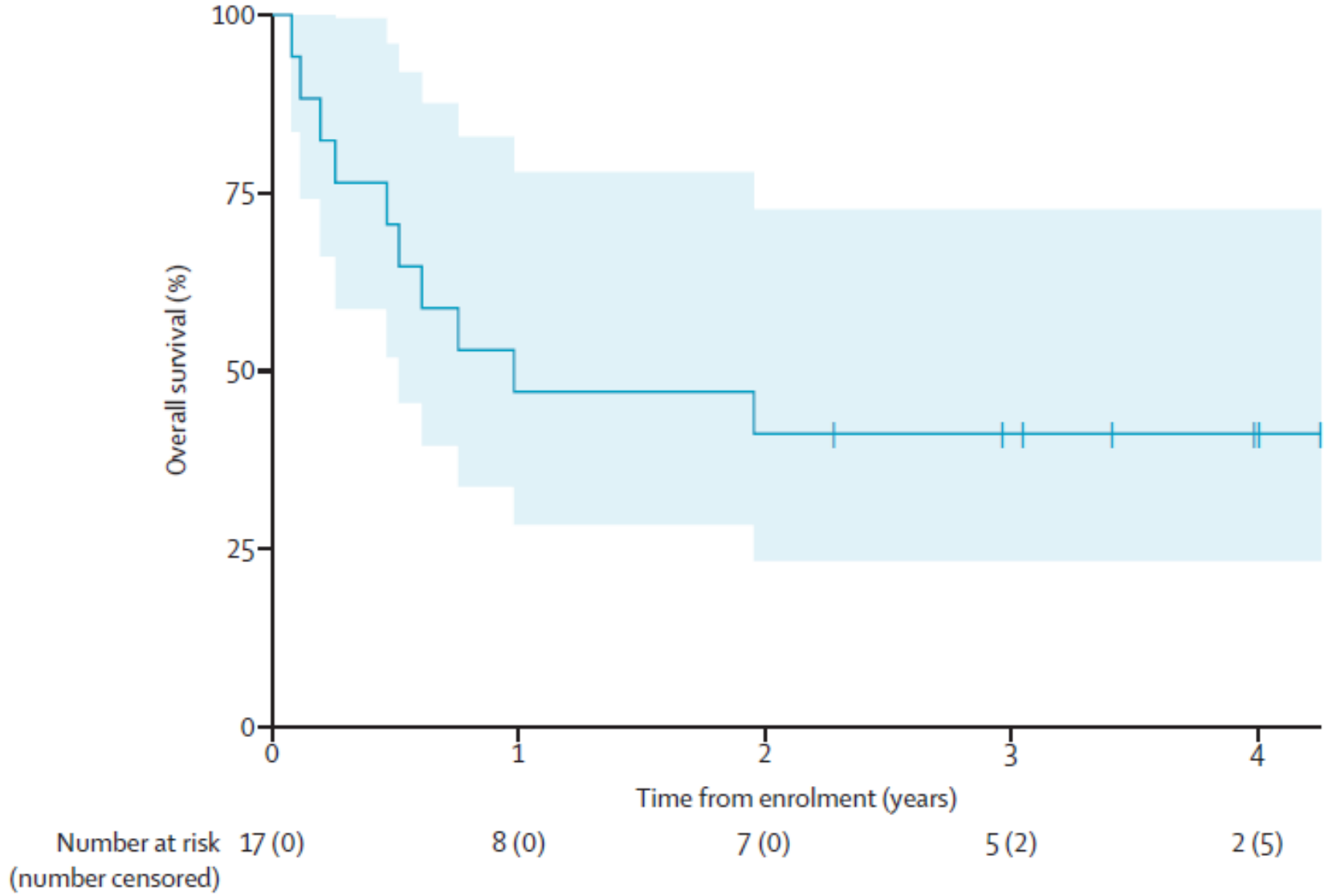
Blast crisis treatment

Disease status	
De novo	10 (59%)
Progression	7 (41%)
Extramedullary disease	
Yes	2 (12%)
No	15 (88%)
Previous tyrosine-kinase inhibitor	
Imatinib	7 (41%)
Dasatinib	1 (6%)
Nilotinib	1 (6%)
Bosutinib	1 (6%)
Imatinib first line, dasatinib second line	1 (6%)
Nilotinib first line, dasatinib second line	1 (6%)
None	5 (29%)



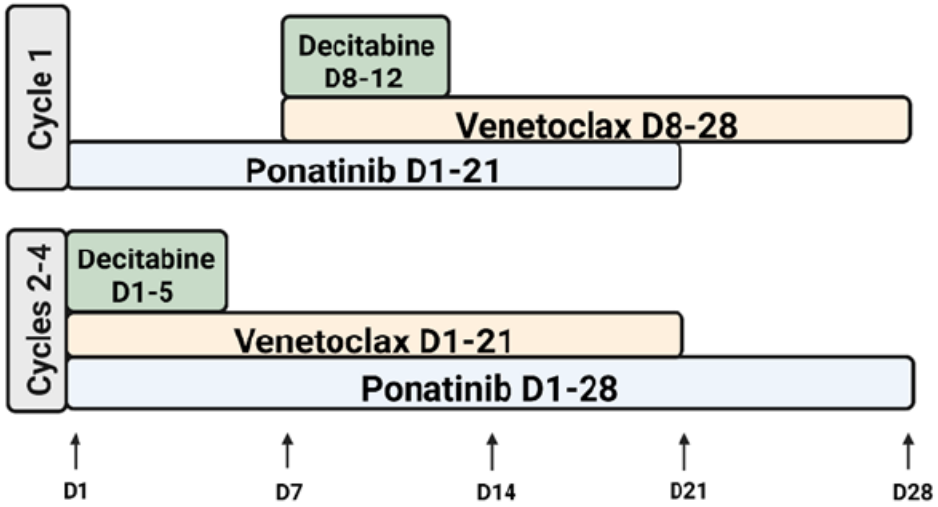
M Copland et al.: Lancet Hem 2021

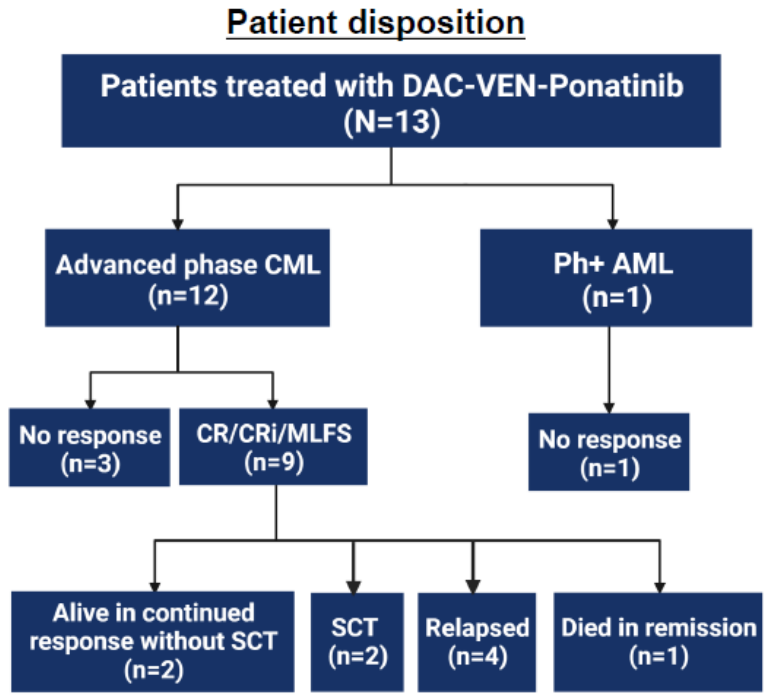
Blast crisis treatment



M Copland et al.: Lancet Hem 2021

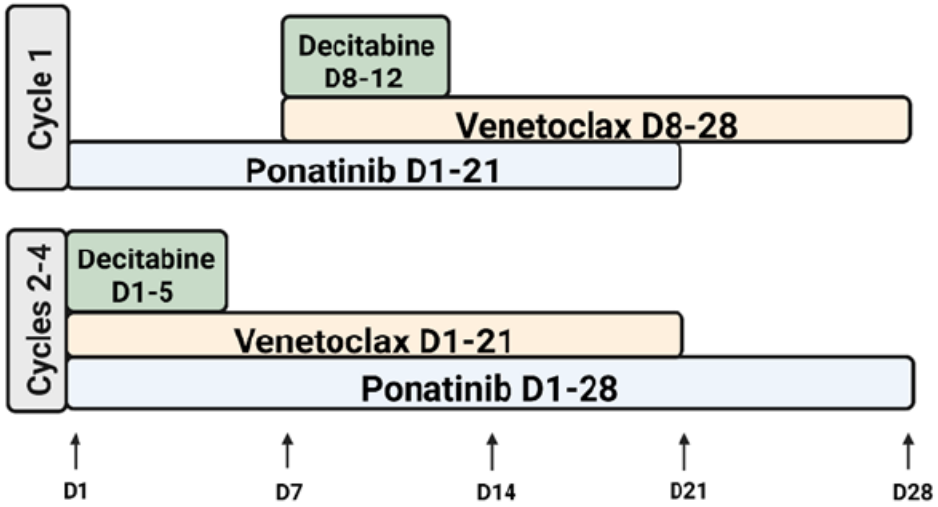
J Senapati: A Phase II Study of the Combination of Decitabine, Venetoclax and Ponatinib in Patients with CML MBP or Ph+ AML



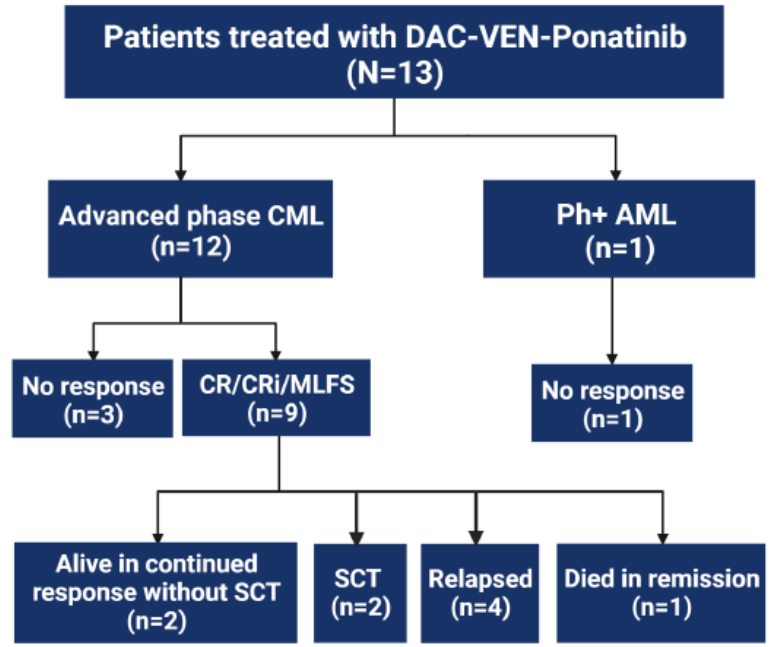


J Senapati et al. ASH 2022

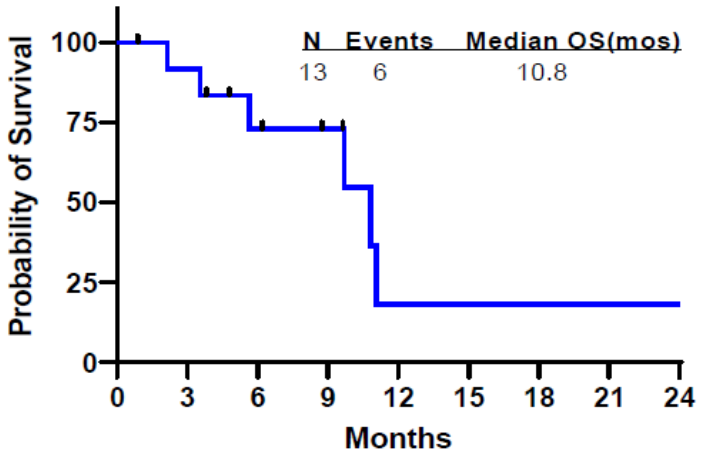
J Senapati: A Phase II Study of the Combination of Decitabine, Venetoclax and Ponatinib in Patients with CML MBP or Ph+ AML



Patient disposition

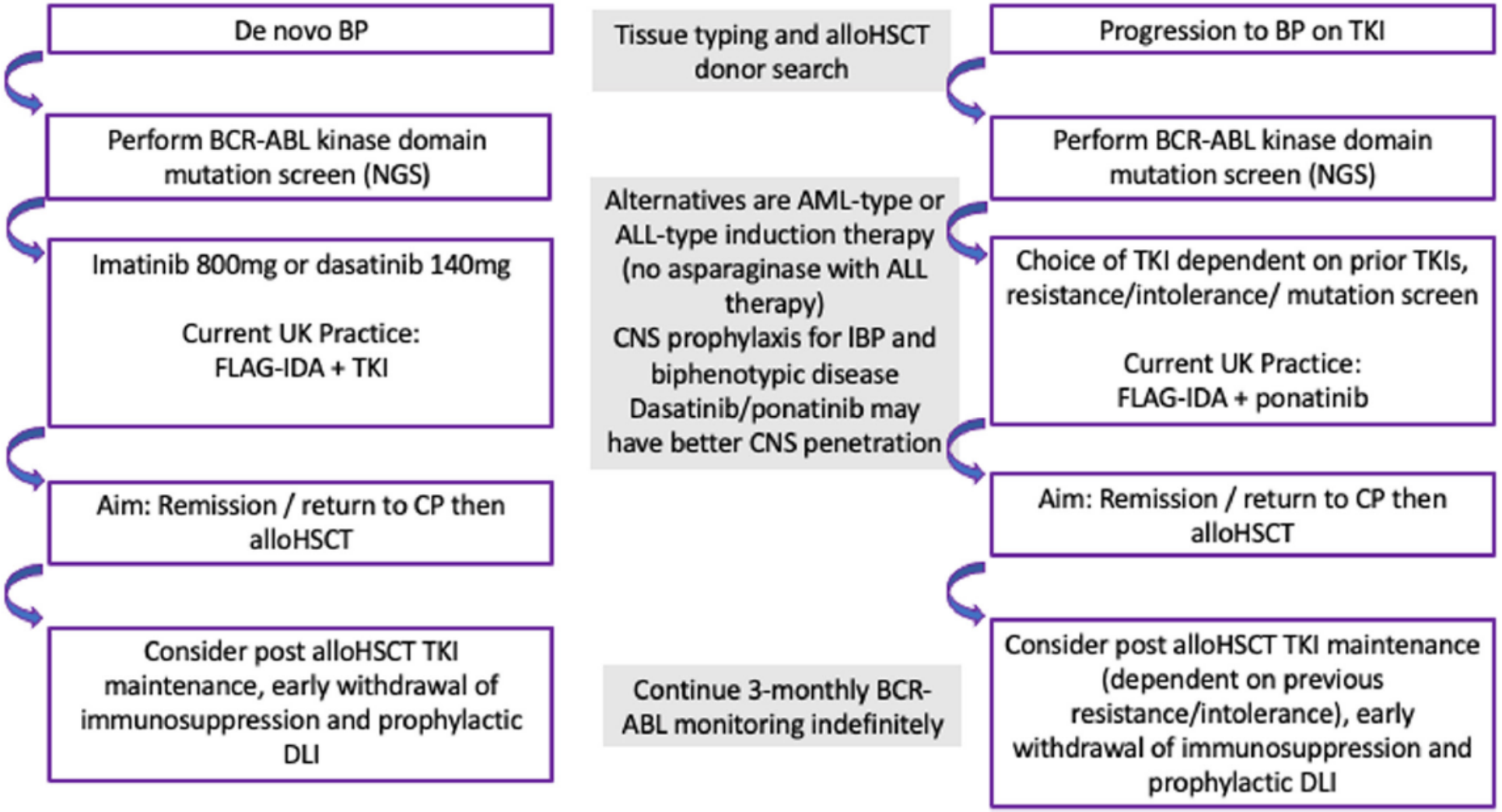


Overall survival of the whole cohort



J Senapati et al. ASH 2022

Treatment algorythm



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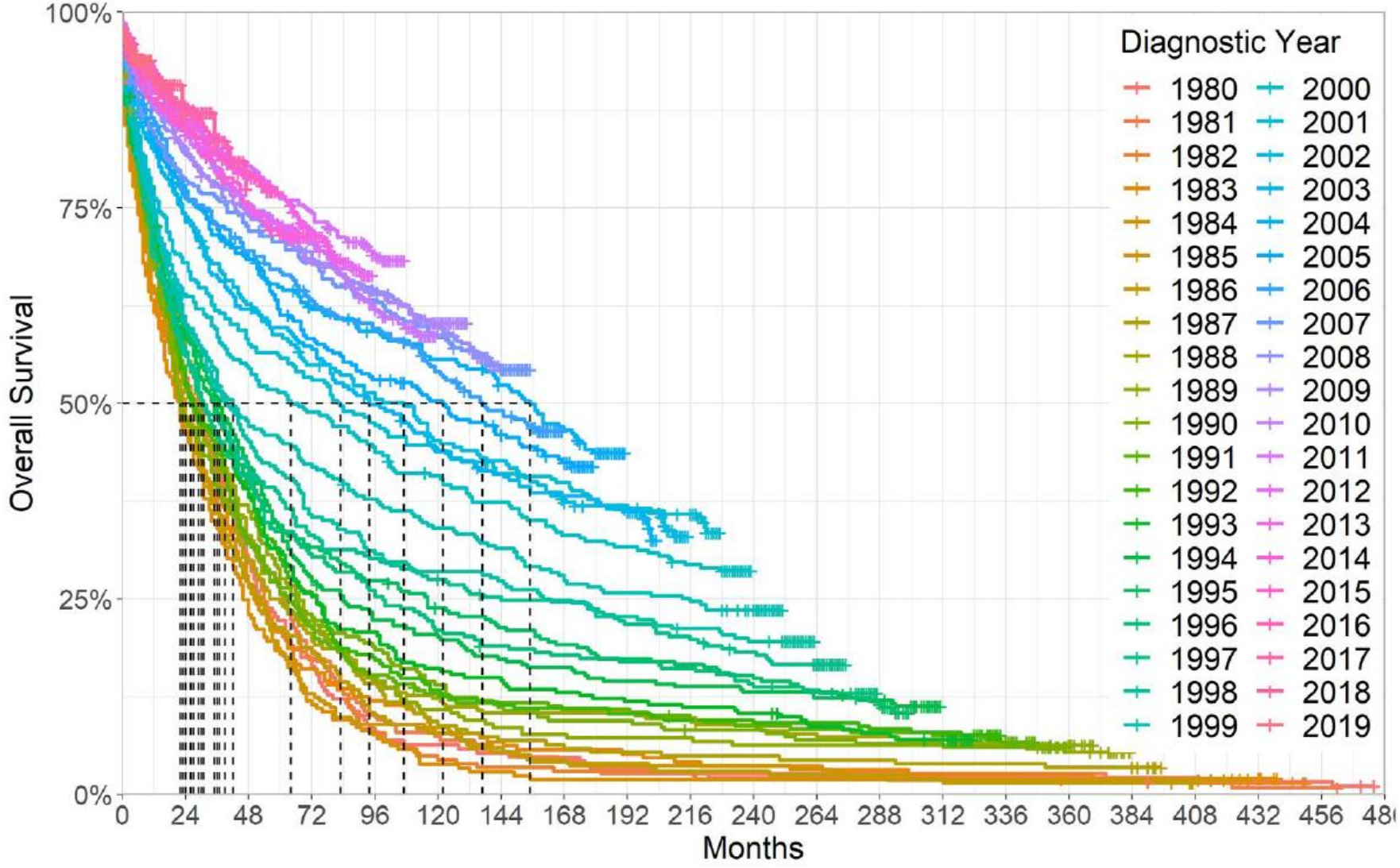
Conclusion

- Treatmentoptions of CML in blast crisis remains unsatisfactory
- Allo-transplantation should be the primary goal of therapy in patients suitable for transplantation
- TKI monotherapy of blast crisis is not sufficient and should be substituted by TKI + CTX approaches
- Treatment of blast crisis is an individual approach and depends on allo-tx availability, clinical condition and biological features of the underlying case

Thank you very much!

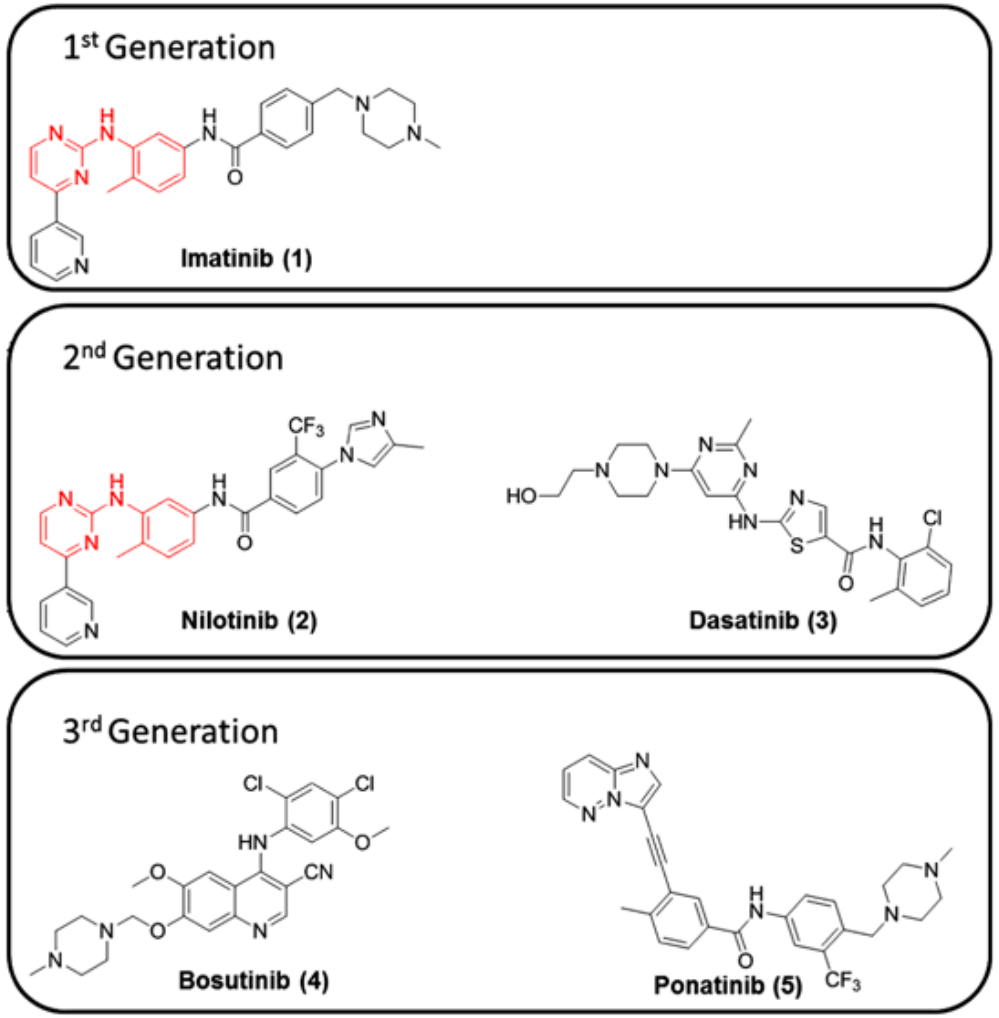
cml@charite.de

Prognose 1980 - 2019

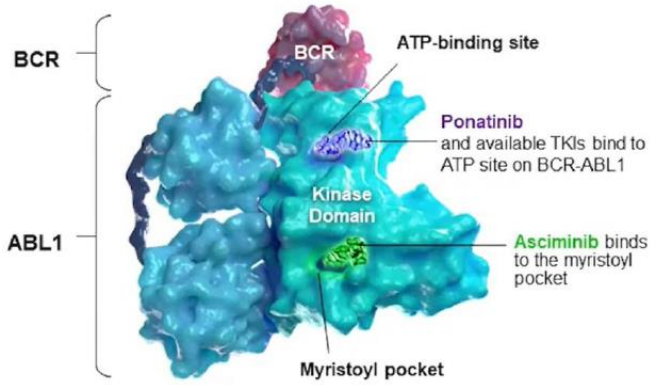


K Sasaki et al.: Cancer 2023

Zugelassene Tyrosinkinaseinhibitoren



- Imatinib 400 mg
- Nilotinib 2 x 300 mg
- Dasatinib 100 mg
- Bosutinib 400/500 mg
- Ponatinib 45 mg

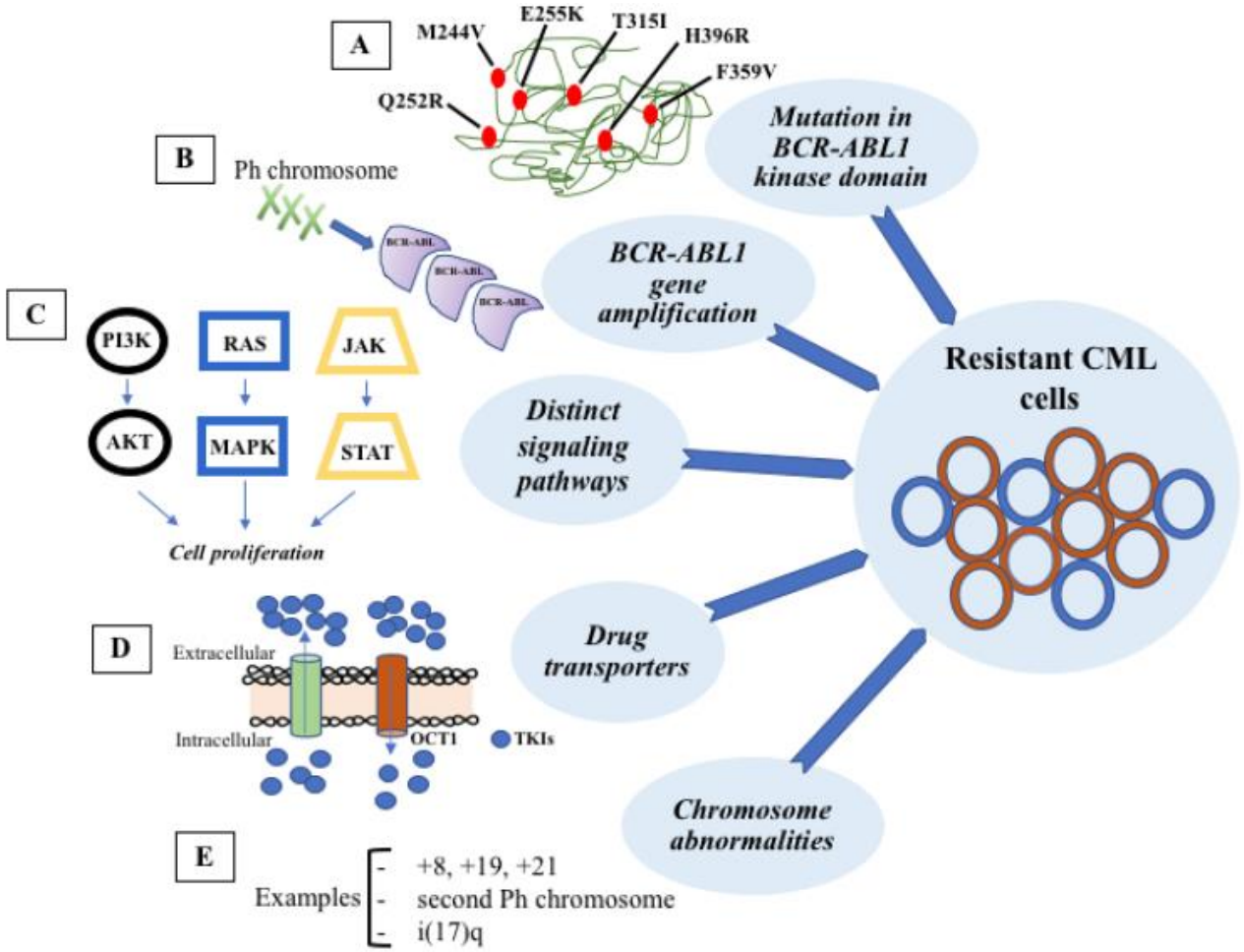


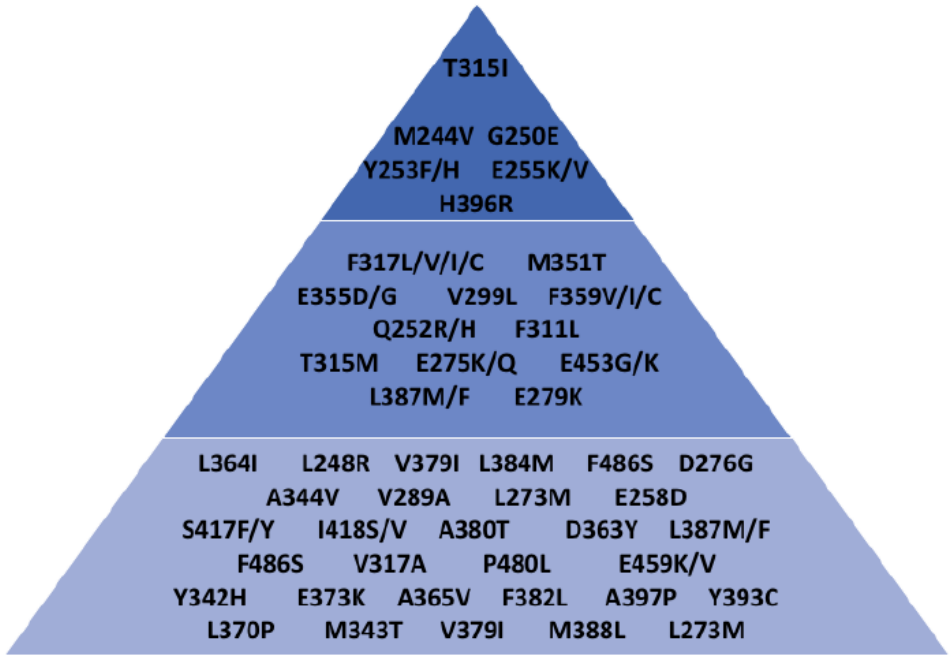
- Asciminib 2 x 40 mg

STAMP: (Specifically Targeting the ABL Myristoyl Pocket)

FC Vasconcelos et al.: Med Chem Res 2017

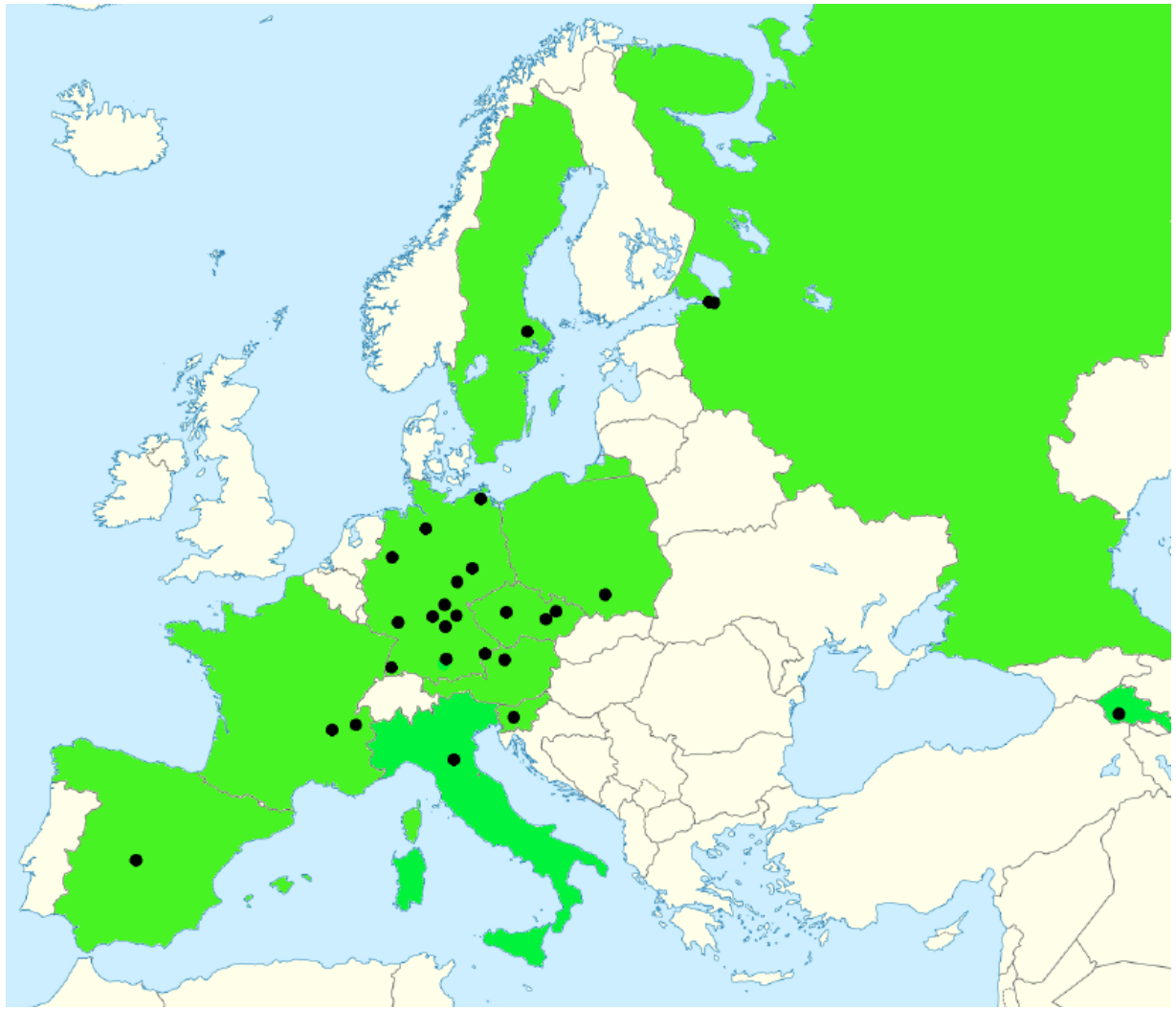
Resistenzmechanismen





G P Amarante-Mendes et al.: Pharmaceutics 2022

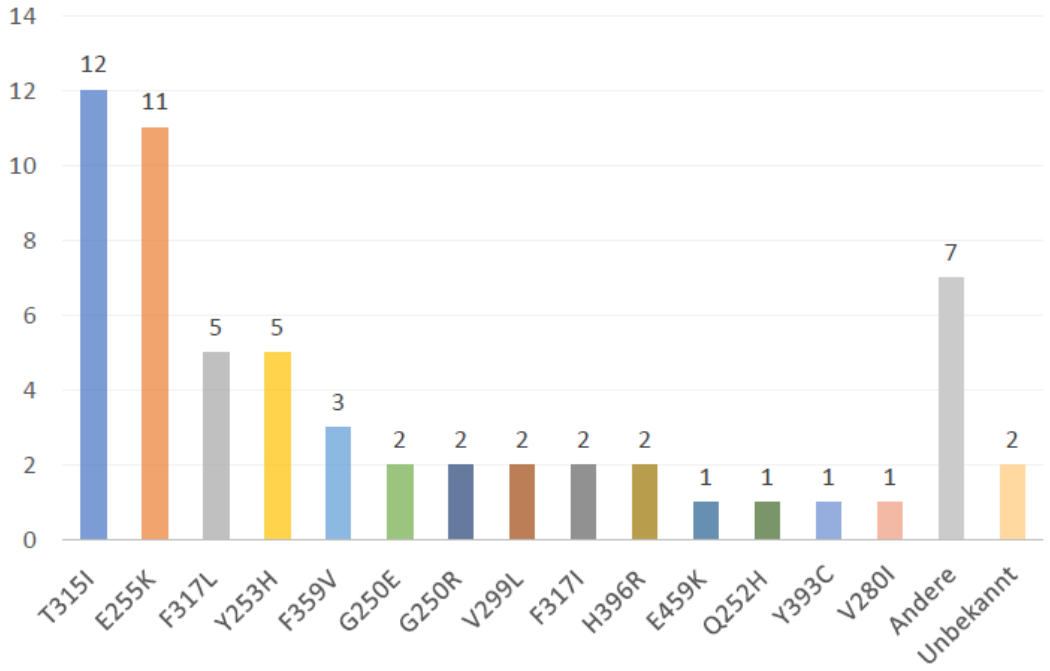
Blast Crisis Registry



Courtesy of A Brioli, Greifswald, 2023

Mutations

BCR::ABL1 - mutations



11 Pat. > 1 mutation

Mutations other than *BCR::ABL1* N=30

Mutation	Frequency
WT1	5
RUNX1#	1#+3
ASXL1#	1#+1
FLT3-ITD#	1
FLT3-TKD	1
BCORL1§	1
IDH1§	1
KRAS#	1
NRAS°	1°
CBFB:MYH11	1
MECOM	1
JAK2##	1
NPM1	1

Mutation	Frequency
TP53°, @	1+1°+1@
ZRSR2°	1
EZH2°	1
STAG2@	1
GATA2	1
NOTCH1##	1
EV1 Überexpression	1

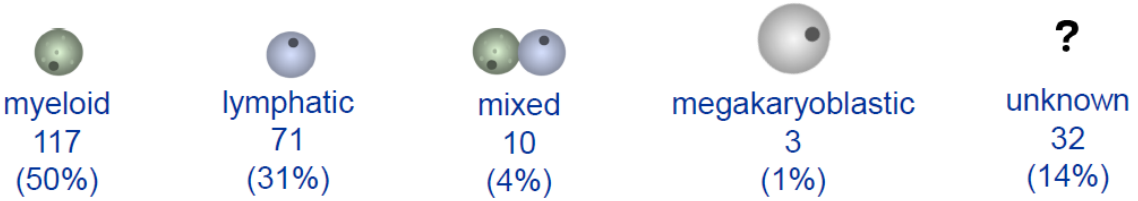
§ # ° @ ## jeweils gleiche*r Pat.

5 Pat. > 1 mutation

Courtesy of A Brioli, Greifswald, 2023

Blast Crisis Patients: Characteristics

Morphology; N=233



BCR::ABL1 Transcript; N=129

e13a2 / e14a2
117

e1a2 / e6a2 / e8a2 /
e19a2/ e13a3
12

Courtesy of A Brioli, Greifswald, 2023