EHA&EuroBloodNet Spotlight on Hypereosinophilic Syndrome

Myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions

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EHA EUROPEAN HEMATOLOGY ASSOCIATION

European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

Conflicts of interest

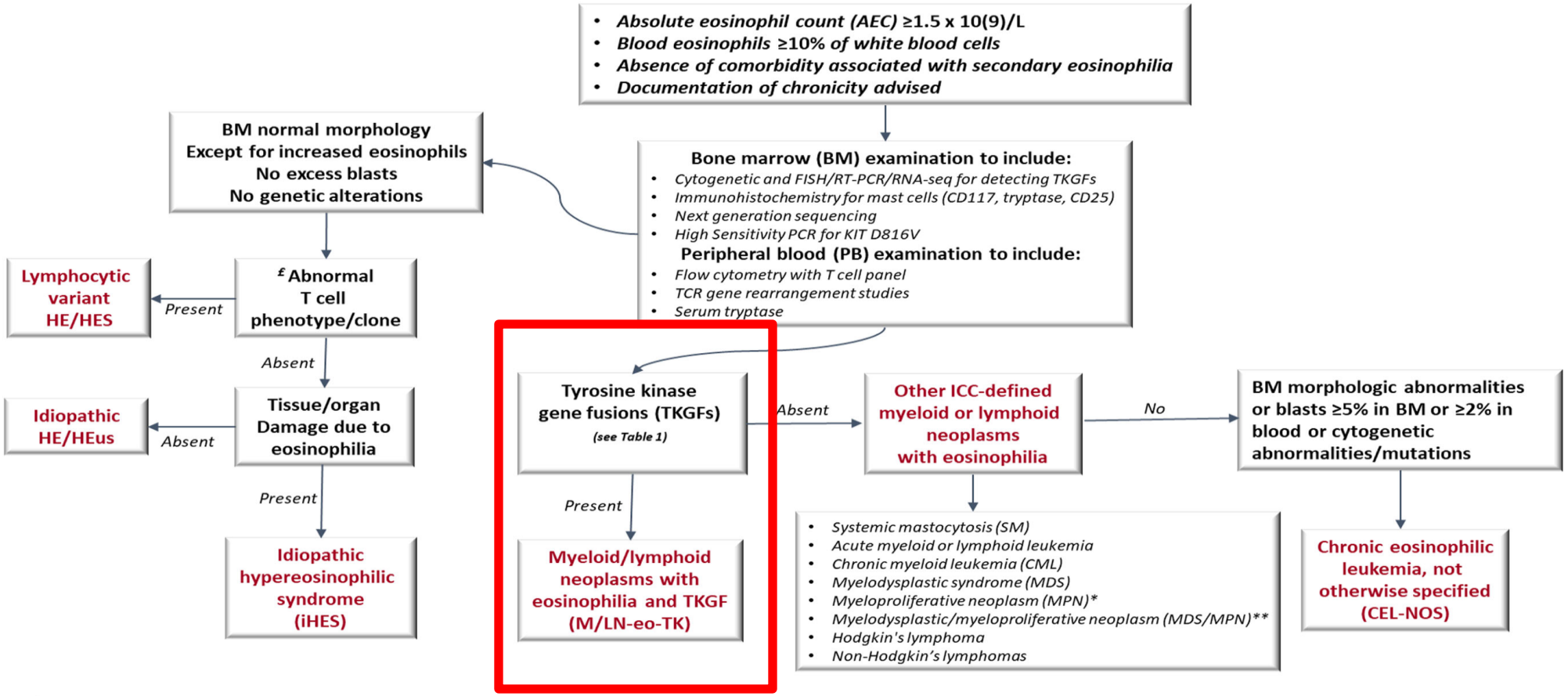
Honoraria by Novartis, Incyte, BMS, Pfizer, GSK

- 50-year-old patient who comes to the emergency room for left side pain and leukocytosis (40% eosinophils). He denies allergies. On chest CT, lateral arch fracture of the third left rib
- Splenomegaly (18 cm)
- *BCR::ABL1* negative
- Performs molecular analysis from SVP: WT1 +, *FIP1L1/PDGFRa* +
- During the screening for molecular tests, she started HU 2 g/day
- Since June 2016, imatinib 400 mg/day for one month with rapid control of WBC. Since July 2016 imatinib 100 mg/day.
- In December 2016, the molecular analysis resulted negative

- Currently continuing imatinib 100 mg in molecular remission

International classification of HE

The International Consensus Classification (ICC) for Hypereosinophilia (HE)



£The abnormal T cells should be detected by flow cytometry and may be confirmed by TCR clonality study.
A diagnosis of CEL, NOS will take precedence over *MPN-unclassifiable, **MDS/MPN-not otherwise specified and atypical chronic myeloid leukemia (aCML) but not chronic myelomonocytic leukemia (CMML)

Wang et al, Am J Hematol 2023

Rearranged eosinophilia

TK gene	Most common fusion	Partner genes/ variants	Typical clinical and BM manifestations	Targeted therapy
PDGFRA	Cryptic deletion at 4q12/ *FIP1L1::PDGFRA*	*CDK5RAP2; STRN; KIF5B; TNKS2; ETV6, BCR*	Common: CEL-like BM with frequent extramedullary involvement Others: B-ALL/LL, AML or mast cell proliferations	Excellent response to TKI
PDGFRB	t(5;12)(q32;p13.2)/ *ETV6::PDGFRB*	>30 partners, cryptic	Common: CEL-like or monocytosis with eosinophilia Others: ALL/LL, AML or mast cell proliferations	Excellent response to TKI
FGFR1	t(8;13)(p11.2;q12.1)/ *ZMYM2::FGFR1*	15 other partners including *BCR*	Common: Extramedullary T-ALL/ LL with BM MPN-like or blast phase of MPN; Others: B-ALL/LL, myeloid sarcoma, AML or MPAL	High rate of response to FGFR inhibitor such as pemigatinib, especially for cases in chronic phase
JAK2	t(8;9)(p22;p24.1)/ *PCM1::JAK2*	*ETV6* and *BCR*	Common: MPN or MDS/MPN-like BM with eosinophilia Others: B- and T-ALL/LL with BM MPN	Limited responses to ruxolitinib
FLT3	t(12;13)(p13.2;q12.2)/ *ETV6::FLT3*	*ZMYM2, TRIP11, SPTBN1, GOLGB1, CCDC88C, MYO18A, BCR*	T-ALL/LL or myeloid sarcoma with CEL-like or MDS/MPN BM features	Various responses to specific FLT3 inhibitors
ETV6::ABL1	t(9;12)(q34.1;p13.2)/ *ETV6::ABL1*	Unknown	CML-like with frequent eosinophilia in chronic or blast phase	Various responses to second generation TKI

Arber et al Blood 2022

- *PCM1::JAK2* category is now called JAK2 rearrangement

- 3 new entities
- M/L-eo with FlT3 rearrangement
- M/L-eo with *ETV6::ABL1*
- M/L-eo with other TK gene fusions

- Constitutive tyrosine kinase signalling as a result of a gene fusion
- Origin from mutated pluripotent bone marrow stem cells that can differentiate into myeloid and/or lymphoid progenitors, leading to clinically complex and heterogenous manifestations
- Frequent association with peripheral blood and/or bone marrow eosinophilia (but not an invariable features)
- Excellent responses, in the majority of cases, to specific TK inhibitors

Wang et al Am J Hematol 2023;
Morales-Camacho et al Cancers 2023

- M/L-eo TK manifest with a very broad range of histological types, most frequently as a chronic myeloid neoplasm, MDS or mixed MDS/MPN, but also as acute myeloid leukemia (AML), mixed acute leukemias (MPAL), B- or T-acute lymphoblastic leukemia.

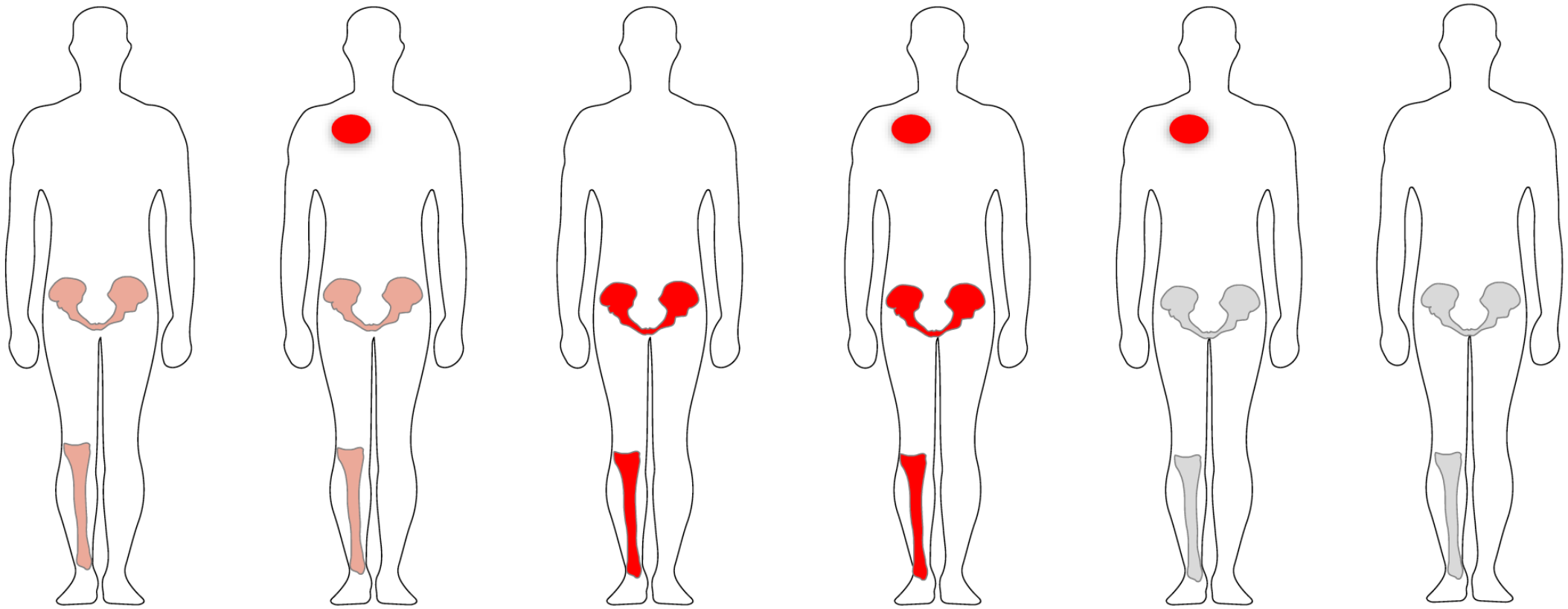
- Extramedullary localization are common.

- Bone marrow may exhibit an atypical (usually interstitial) infiltrate of mast cells in the absence of the KIT816V mutation.

- The estimated incidence is <1/100.000 person, rare in children.

Wang et al Am J Hematol 2023;
Morales-Camacho et al Cancers 2023

Heterogeneity of clinical presentation



BM/PB: Chronic Phase* No EMD

BM/PB: Chronic Phase* with EMD

BM/PB: Blast Phase No EMD

BM/PB: Blast Phase with EMD

EMD Only

Treated, no morphologic or radiologic evidence of disease; + Cytogenetic/FISH, or molecular evidence of *FGFR1* rearrangement

Gotlib, Hematology 2022

- Highly variable
- Peripheral eosinophilia present in approximately 70% of cases, most common in PDGFRa and ETV6::ABL1 forms

- Presentation as chronic myeloid neoplasm: often increased fibrosis, megakaryocytes significantly reduced, increased, or normal MPN-like (abnormal segmentation) or MDS-like (small and hypolobated).

- Initially described in PDGFRA forms, atypical mast cells spindle or round, with aberrant CD25 expression, scattered and in loose aggregates. In a minority of cases, could resemble SM-AMN before to detect TK fusion.

Wang et al Am J Hematol 2023;
Morales-Camacho et al Cancers 2023
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- A minor proportion of patients present with acute leukemia, and the underlying chronic myeloid neoplasm only becomes evident post-chemotherapy.

- Extramedullary infiltrates or tumoral lesions are frequent, commonly involving epidural and/or paraspinal space, or lymph nodes.

- These extramedullary lesions can be T-ALL/LBL (lymphoblastic lymphoma), B-ALL/LBL, myeloid sarcoma or blasts with a mixed phenotype (MPAL), or rarely a mature T-cell lymphoma, and often with various eosinophilic infiltrates.

Wang et al Am J Hematol 2023;
Morales-Camacho et al Cancers 2023
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Somatic mutations

- Mutations are reported in 20%–50% of cases of M/LN-eo with **PDGFRA** including ASXL1, BCOR, DNMT3A, ETV6, SRSF2, and RUNX1.
- In M/LN-eo with **PDGFRB** (30%–50%) mutations involving ASXL1, TET2, BCOR, ETV6, STAG2, and RUNX1 gene
- In ***PCM1::JAK2*** M/LN-eo, mutations are reported in 14%–50% of cases, involving ASXL1, TET2, BCOR, RUNX1, SRSF2, ETV6, TP53.
- In M/LN-eo with ***ETV6::ABL1***, although data are also limited, mutations involving ARID2, TP53, SETD2, CDKN1B, PTPN11, and SMC1A genes have been reported in approximately 50% of cases.
- In M/LN-eo with **FLT3 fusions**, mutations of ASXL1, PTPN11, RUNX1, SETBP1, SRSF2, STAT5B, TET2, TP53, and U2AF1 genes have been reported in approximately 40%–50% of cases.
- The biological role of co-operating mutations in M/LN-eo-TK is overall unclear except for M/LN-eo with **FGFR1** where mutations are detected in 70%–80% of cases with around 80% of them involving RUNX1.

Wang et al Am J Hematol 2023;
Morales-Camacho et al Cancers 2023

PDGFRa: series of pts evaluating imatinib

Reference	n	CHR (%)	CMR (%)	Follow-up in months median (range)	Resistance	Deaths
Baccarani *et al.*, *Haematologica*, 2007 [27]	27	100	100	25 (15-60)	-	-
Klion *et al.*, *J Allergy Clin Immunol*, 2009 [34]	17	N/A	88	N/A	-	-
Helbig *et al.*, *Hematol Oncol*, 2010 [33]	16	100	100	36 (2-59)	-	-
Pardanani *et al.*, *Leukemia*, 2012 [31]	18	94	100	73	1	2
Legrand *et al.*, *Medicine*, 2013 [32]	44	100	95	52 (1-100)	-	1
German Registry on Disorders of Eosinophils and Mast Cells	64	100	90	77 (2-129)	2	4

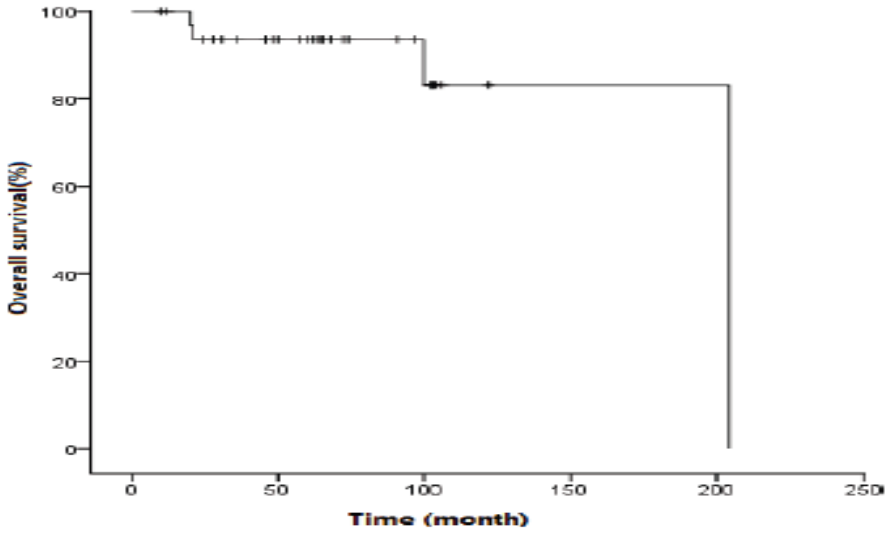
- Weekly imatinib 100 mg after achievement of PCR negativity can maintain deep responses

Reiter and Gotlib Blood 2016

- Annual incidence estimated at around 0.18 cases per million
- Most common with cryptic interstitial deletion in 4q12 (observed with FISH and RT-PCR) and FIPL1::PDGFRA fusion gene
- Other partners have been reported, such as KIF5B, CDK5RAP2, ETV6, BCR, TNKS2, FOXP1
- Presented as usually as MPN with eosinophilia in >95% of cases or CEL-like with extramedullary involvement
- Male/female ratio 17:1; median age late ‘40s
- Extremely sensitive to low dose imatinib

Wang et al Am J Hematol 2023

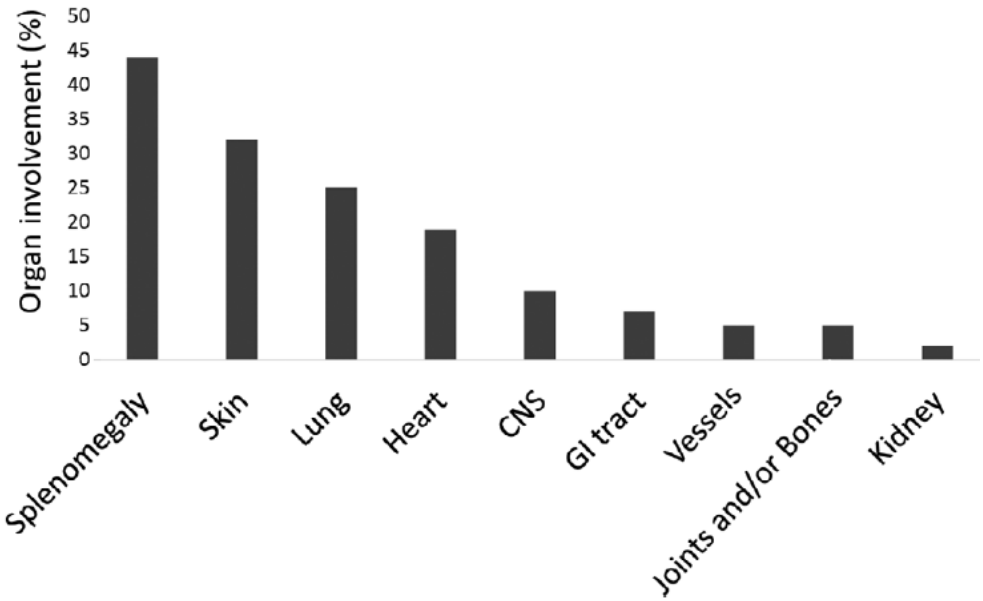
- 33 patients FIP1L1/PDGFRa rearranged treated with imatinib
- Median FU 64 months
- CHR: 94% (after a median of 3 months)
- RT-PCR : 97% CMR (median time to response 3 months)
- 3 resistant cases: onset of T674I mutation
- 8 patients discontinued: 50% relapsed. 2 pts developed secondary resistance.
- 50% in molecular remission after + 47 months from discontinuation.



Qu et al. Oncotarget 2016

Large series of 151 PDGFRA rearranged French patients

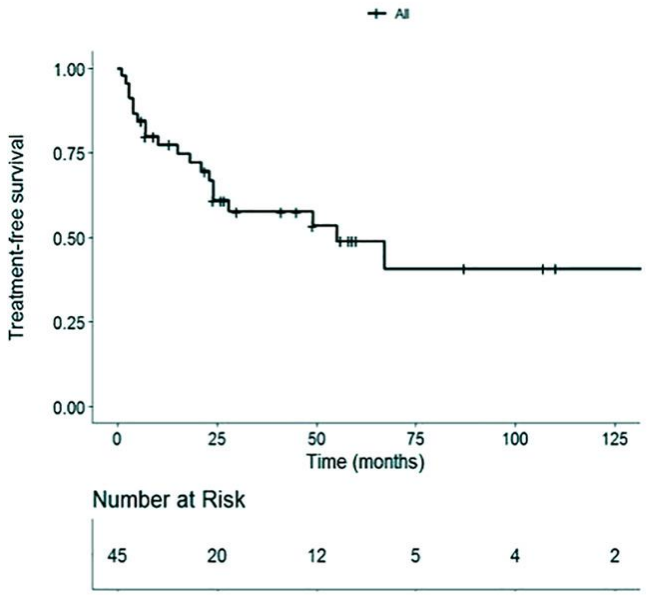
Patients	N = 151
Male	143 (96)
Age at diagnosis	49 +/– 12
Number of organs involved	
Asymptomatic	26 (17)
1	41 (28)
2	36 (24)
3 or more	31 (21)
CBC	
Eosinophils (/mm3)	10 309 +/– 5960
Hemoglobin (g/dl)	13 +/– 2
Platelets (/mm3)	195 700 +/– 63 600
Neutrophils (/mm3)	6850 +/– 5330
Lymphocytes (/mm3)	2650 +/– 1120
Basophils (/mm3)	240 +/– 270
Monocytes (/mm3)	640 +/– 415
F/P transcript screening	
PCR	140/140 (100)
FISH	87/87 (100)

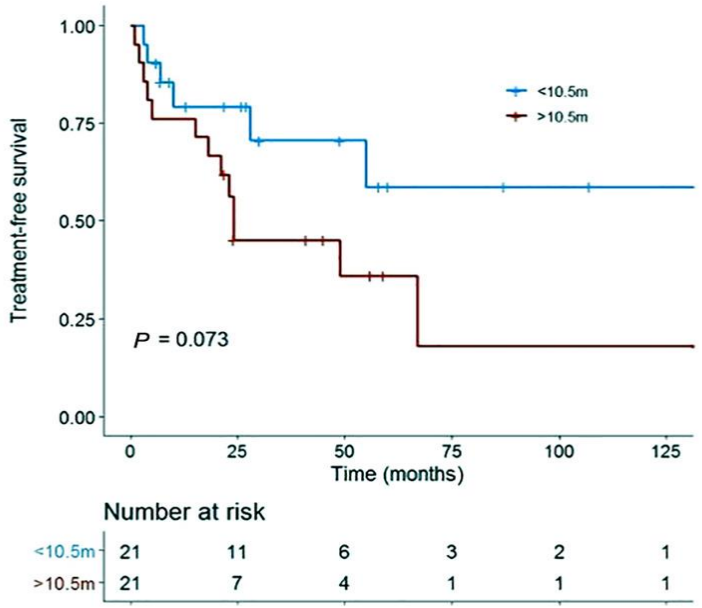


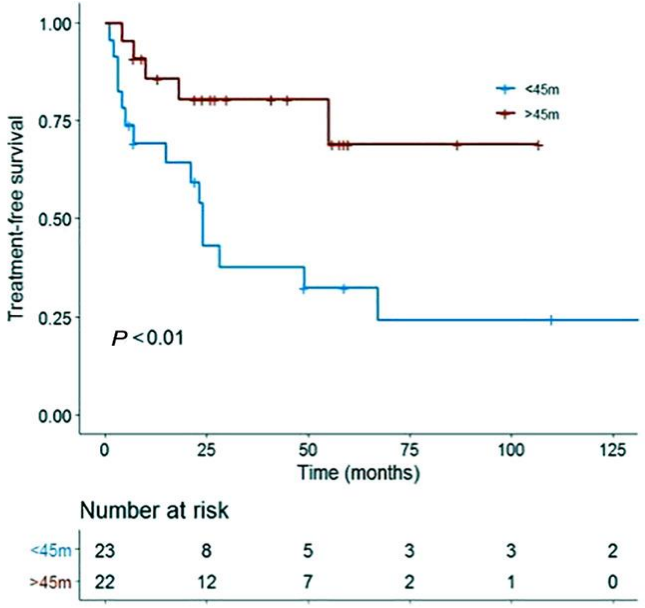
- B12 and tryptase levels were elevated in 94% and 79%
- 10-year OS was 84%

Rohmer et al Am J Hematol 2020

Predictors of relapse after imatinib discontinuation





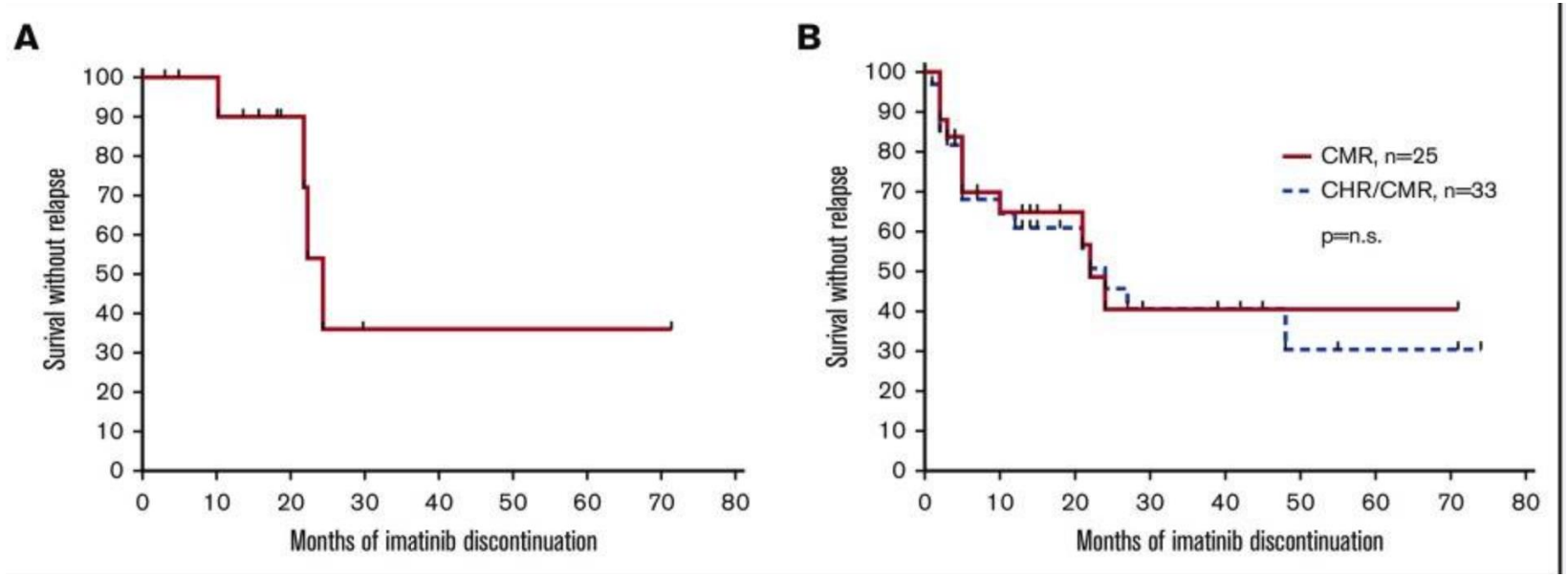


148 patients treated with imatinib after a median time of 11 months from identification

- 96% achieved a complete response
- AEs: muscle cramps, skin rash and cytopenia
- 9 relapses during treatment
- 46 pts discontinued: RFS 57% after a median of 10 months
- The predictor of relapse were the time of imatinib initiation and the total time of treatment

Rohmer et al Am J Hematol 2020

Treatment free remission in PDGFRa imatinib-treated pts



- 12 pts discontinued imatinib after achievement of CMR
- Median time of treatment 80 months and median time of CMR 66 months
- Molecular relapse observed in 4 patients and 3 regained CMR
- Molecular relapse free survival at 24 months was 65%

Metzgeroth et al Blood Adv 2020

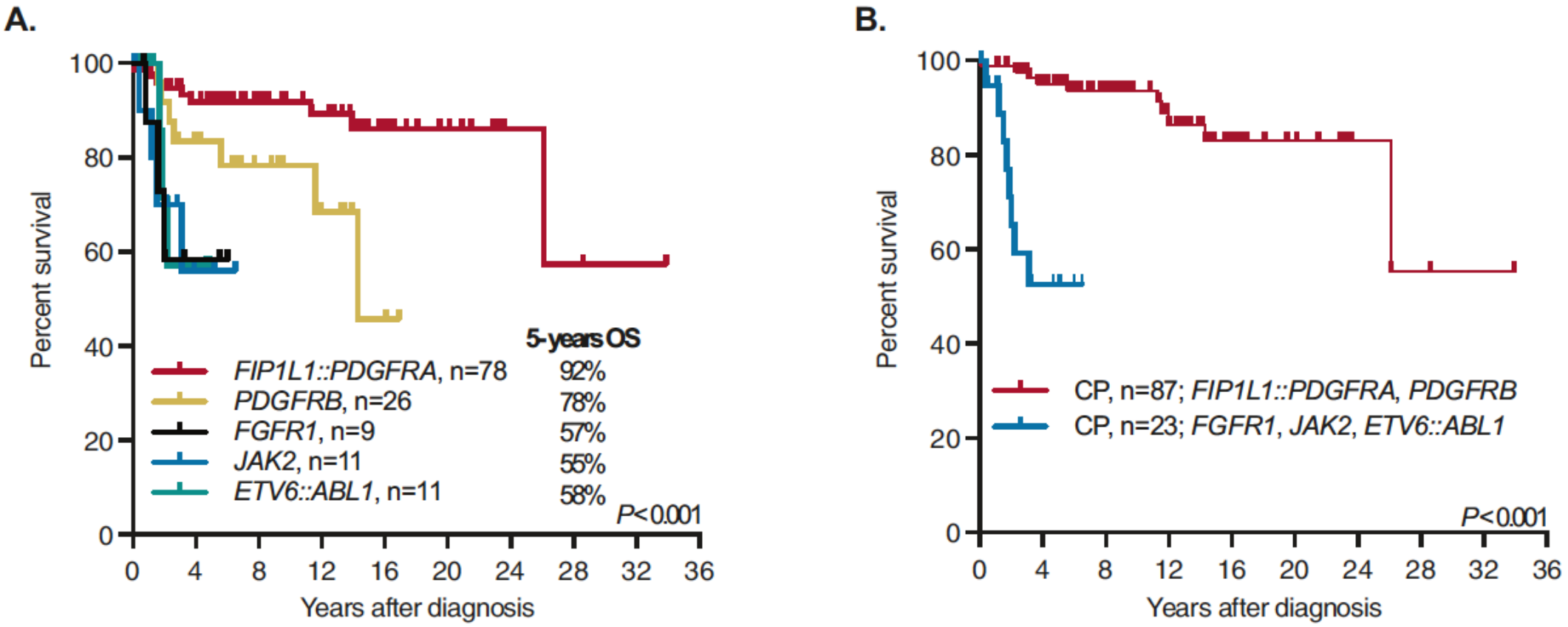
Registry-based cohort and blast phase characteristics

	No. of patients	Partner genes	Eosinophilia (*n*) >0.5/>1.5 × 10^9/l (%)	Monocytosis >1 × 10^9/l	Overall survival
FIP1L1::PDGFRA	78	1	44 100%/91%	44 27%	92% at 5 years 92% at 10 years
PDGFRB	26	11	16 75%/50%	16 31%	78% at 5 years 78% at 10 years
FGFR1	9	3	6 50%/16%	6 33%	57% at 5 years
JAK2	11	2	8 75%/50%	8 25%	55% at 5 years
ETV6::ABL1	11	1	7 100%/100%	7 85%	58% at 4 years

Fusion gene	*n*	Primary BP	CP at diagnosis	Secondary BP	Myeloid		Lymphoid	
					BM (primary/ secondary)	EMD (primary/ secondary)	BM (primary/ secondary)	EMD (primary/ secondary)
FIP1L1::PDGFRA	78	13	65	4	10 (8/2)	4 (3/1)	–	3 (2/1)
PDGFRB[a]	26	4	22	1	1 (0/1)	1 (1/0)	1 (1/0)	2 (2/0)
FGFR1[a]	9	6	3	1	–	2 (2/0)	2 (1/1)	3 (3/0)
JAK2[a]	11	0	11	3	1 (0/1)	–	2 (0/2)	–
ETV6::ABL1	11	2	9	4	2 (0/2)	2 (1/1)	1 (0/1)	1 (1/0)
Overall	135	25	110	13	14 (8/6)	9 (7/2)	6 (2/4)	9 (8/1)

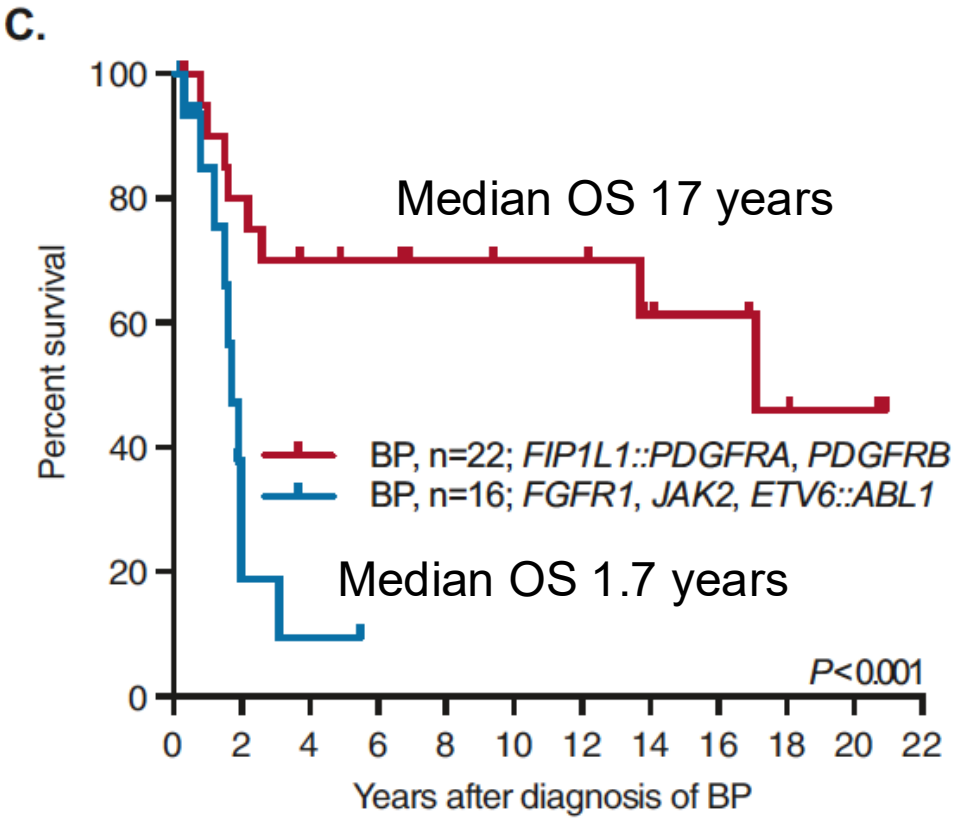
Monocytosis could be observed in PDGFRA (33%) and ETV6::ABL1 (85%) patients

Registry-based cohort: overall survival of CP patients

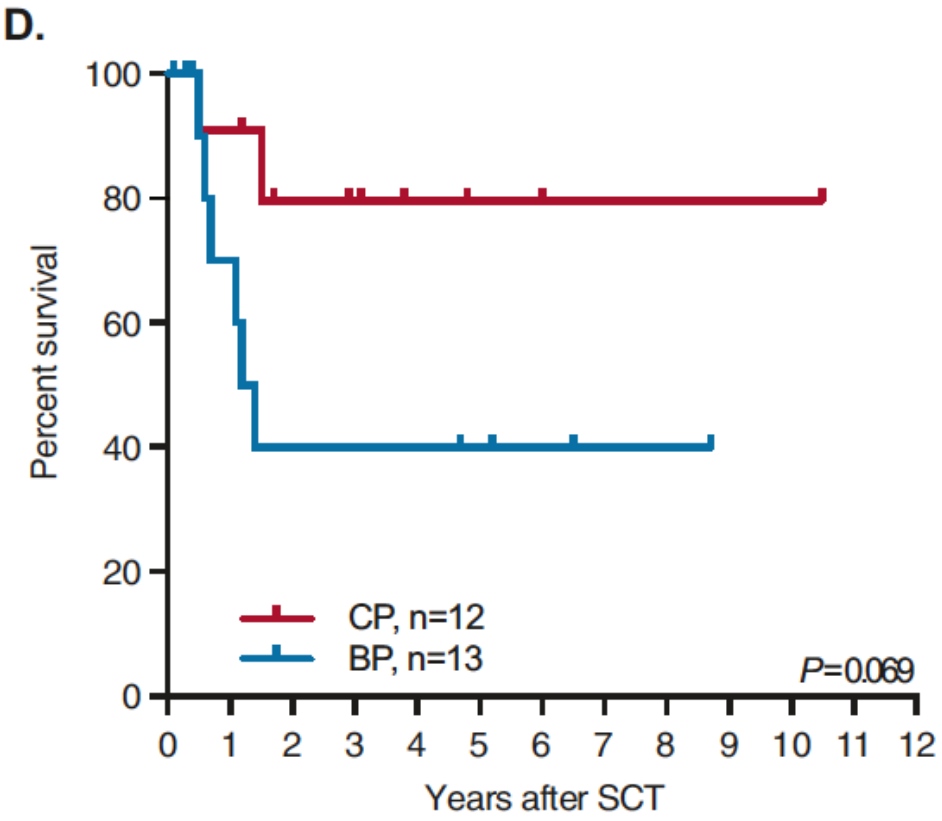


Metzgeroth et al Leukemia 2023

Registry-based cohort: overall survival of CP patients



OS from diagnosis of BP



OS from allogeneic HSCT

European Reference Network for rare or low prevalence complex diseases

Network Hematological Diseases (ERN EuroBloodNet)

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Metzgeroth et al Leukemia 2023

Webinars EuroBloodNet

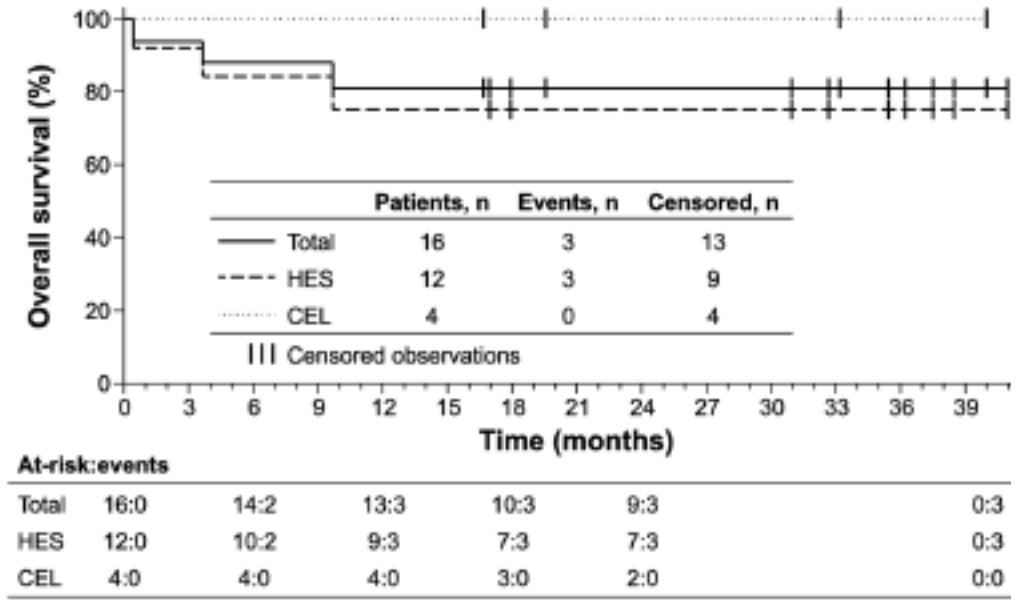
Mutations associated to resistance to imatinib

- Two specific mutations have been reported as main cause of resistance to imatinib: **T674I and D842V.**
- Ponatinib is active on both mutants. Also, avapritinib has been tested active against GIST with D842V mutation.

compound	Ba/F3 F/P IC_{50} [nM]	Ba/F3 F/P T674I IC_{50} [nM]	Ba/F3 F/P D842V IC_{50} [nM]
Ponatinib	0.6	9	154
Sorafenib	0-5	10-50	>1000
Imatinib	0-5	>500	>1000
Dasatinib	5-10	>500	1000
Masitinib	8.3	>1000	>1000
Nilotinib	8.5	1736	4093
Midostaurin	10-50	10-50	>500
Sunitinib	52.7	293.9	>1000

Sadovnik et al, Exp Hematol 2014;
Jones et al Eur J Cancer 2021

Treatment of resistant PDGFRA patients with nilotinib



Best Responses and Overall Survival After a Median Follow-up of 32 Months (ITT Population)

	HES (n = 12)	CEL (n = 4)	Total (N = 16)
Best hematologic response			
Overall response, n (%; 95% CI)	1 (8.3; 0.2–38.5)	2 (50.0; 6.8–93.2)	3 (18.8; 4.0–45.6)
CR	1 (8.3)	2 (50.0)	3 (18.8)
PR	0	0	0
Absence of response, n (%)	11 (91.7)	2 (50.0)	13 (81.3)
SD	3 (25.0)	1 (25.0)	4 (25.0)
PD	3 (25.0)	0	3 (18.8)
NE	5 (41.7)	1 (25.0)	6 (37.5)
Overall survival, % (95% CI)			
6 months	83.3 (62.3–100)	100 (100–100)	87.5 (71.3–100)
12 months	75.0 (50.5–99.5)	100 (100–100)	81.3 (62.1–100)
18 months	75.0 (55.5–99.5)	100 (100–100)	81.3 (62.1–100)
24 months	75.0 (50.5–99.5)	100 (100–100)	81.3 (62.1–100)

- 16 pts treated with nilotinib 400 mg BID
- 12 with HES : 1 CHR and 3 with stable disease
- 4 pts with CEL: 3 with CR (but with FIP1L1/PDGFRa)
- Median OS not reached. Most common AEs: pruritus, neutropenia

PDGFRB positive M/L-eo TK: baseline features

- Frequency of 20% of all M/L-eo TK
- Median age late ‘40; male/female ratio 2:1
- Most common presentation: MDS/MPN (more like CMML) or MPN with eosinophilia. PDGFRB also present in myeloid or lymphoid leukemia. Rarely, progression as angioimmunoblastic T-cell lymphoma described.
- Monocytosis is frequent with splenomegaly
- Organ involvement is not frequent
- Excellent response to imatinib

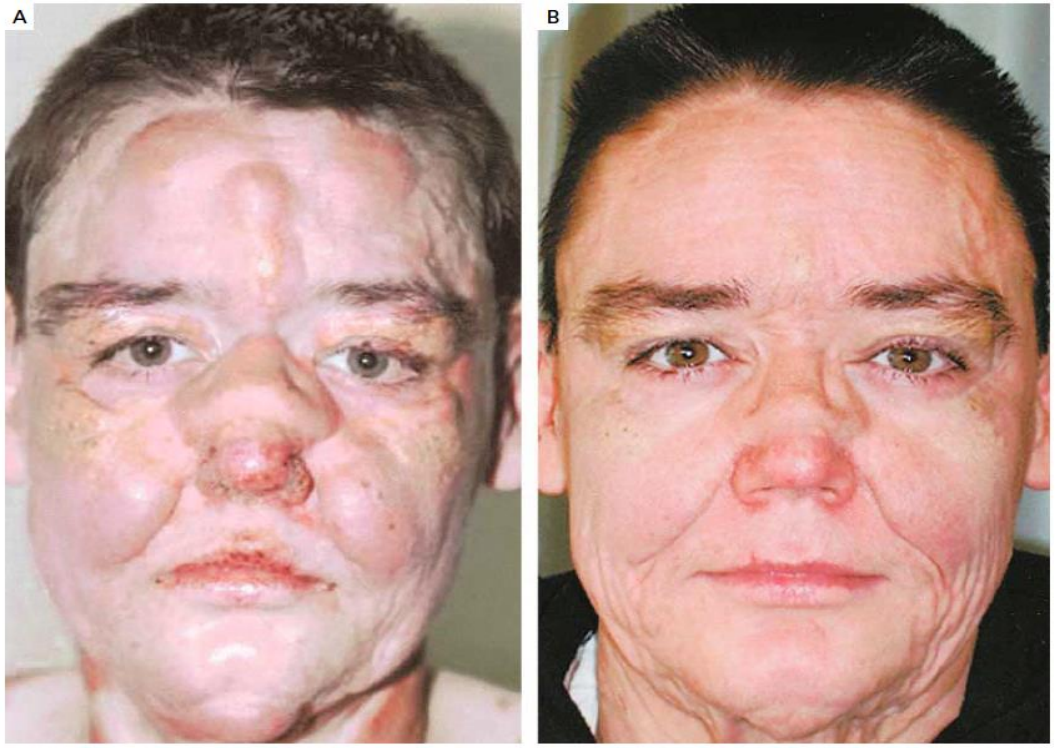
Wang et al Am J Hematol 2023

- The most common genetic variant is related to t(5;12)(q32;p13.2) with *ETV6* as partner gene, followed by *CCD88C::PDGFRB* and the rest mostly reported in individual cases.

- Criptic *PDGFRB* rearrangements are common, frequently occurring in partner genes other than ETV6, such as *BCR, DIAPH1, SART3, 3GBP1*, likely due to small deletions, inversions or alterations within complex karyotypes. Some of the fusions may not even be detected by FISH and required a sequencing.

RESPONSE TO IMATINIB MESYLATE IN PATIENTS WITH CHRONIC MYELOPROLIFERATIVE DISEASES WITH REARRANGEMENTS OF THE PLATELET-DERIVED GROWTH FACTOR RECEPTOR BETA

- 34 patients with t(5;12) but only 4 treated with imatinib
- All 4 patients achieved CHR after 2 weeks, cytogenetic and molecular remission
- Median FU only 1 year



Apperley et al. NEJM 2002

PDGFRB positive M/L-eo TK: long-term FU

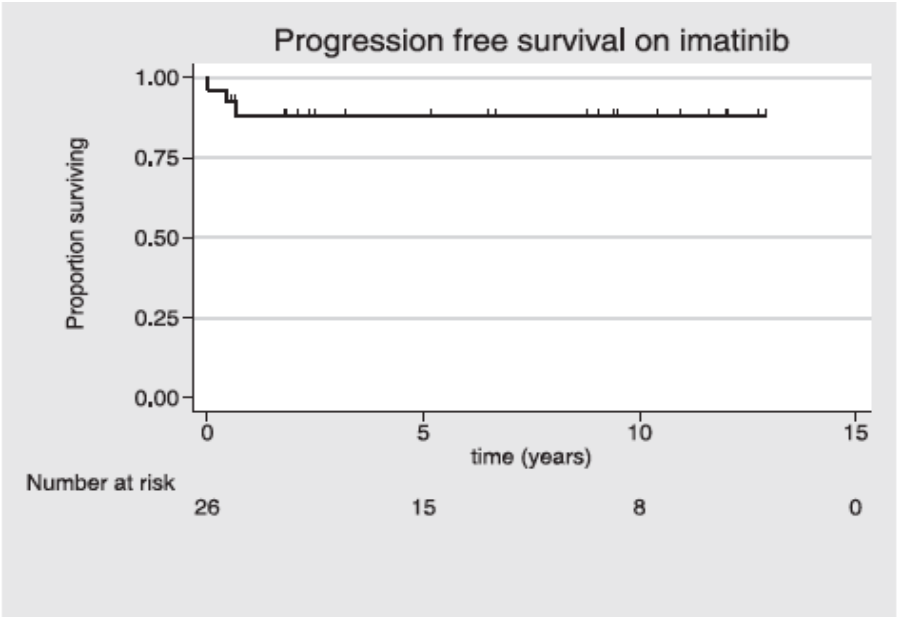
Pt	Age at diagnosis, y	Sex, M/F	WBC at diagnosis × 10^9/L	Eos at diagnosis × 10^9/L	Plts at diagnosis × 10^9/L	Duration of disease, mo	Prior therapy	Cytogenetics	Fusion gene
1	50	M	52	4.8	190	15	None	t(5;12) (q33;p13)	*ETV6-PDGFRB*
2	69	M	41	1.6	192	18	None	t(5;12) (q33;p13)	*ETV6-PDGFRB*
3	32	M	80	7.8	74	54	HU,IFN	t(5;12) (q33;p13)	*ETV6-PDGFRB*
4	51	M	20.6	1.8	245	9	HU, IFN	t(5;12) (q33;p13)	*ETV6-PDGFRB*
5	56	M	80	3.2	91	9	None	t(5;12) (q33;p13)	*ETV6-PDGFRB*
6	36	M	56.9	5.0	114	1	None	t(5;12) (q33;p13)	*ETV6-PDGFRB*
7	57	F	66	5.0	113	2	HU	t(5,12)	*ETV6-PDGFRB*
8	48	M	10.8	8.4	131	16	HU	ins t(2;12) (p21;q?13q?22), del(5)(q33q35)	*ETV6-PDGFRB*
9	6	M	9.3	4.1	506	174	HU, IFN, steroid	t(5;12) (q33;q13)	*PDGFRB* Partner unknown
10	68	M	46.5	12.6	198	25	HU, IFN	t(3;5) (p21,q31)	*PDGFRB* Partner unknown
11	78	M	138	5.4	92	17	HU, IFN, Bu, 6-MP	t(5;15) (q33,q22)	*TP53BP1-PDGFRB*
12	65	F	62	3.5	124	82	HU, Bu, FLAG-Ida	t(1;3;5) (p36;p21;q33)	*PDGFRB* Partner unknown

- 12 patients with t(5;12) all treated with imatinib
- Median duration of treatment 47 months
- 11/12 reached a CHR and 10/12 a CMR

David et al, Blood 2007

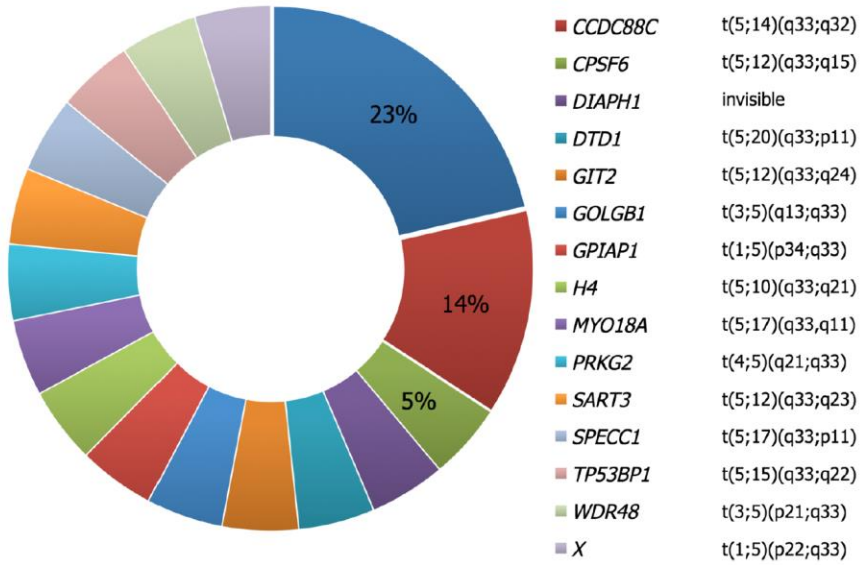
PDGFRB positive M/L-eo TK: long-term remissions with imatinib

- 26 patients with t(5;12) all treated with imatinib
- 18/26 ETV6 as partner of PDGFRβ
- Median FU 10.2 years
- OS at 10 years: 90%
- Overall response rate: 96% (55% cytogenetic response, 36% molecular response)
- None of the pts who achieved a cytogenetic or molecular remission experienced a progression

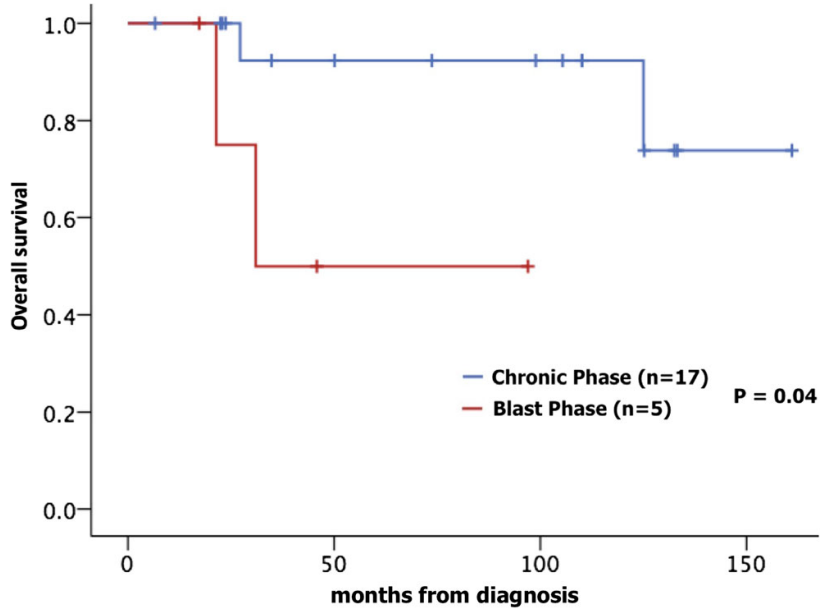


Cheah et al, Blood 2014

PDGFRB positive M/L-eo TK: CP and BP



PDGFRB partner genes	corresponding translocation
ETV6	t(5;12)(q33;p13)
CCDC88C	t(5;14)(q33;q32)
CPSF6	t(5;12)(q33;q15)
DIAPH1	invisible
DTD1	t(5;20)(q33;p11)
GIT2	t(5;12)(q33;q24)
GOLGB1	t(3;5)(q13;q33)
GPIAP1	t(1;5)(p34;q33)
H4	t(5;10)(q33;q21)
MYO18A	t(5;17)(q33,q11)
PRKG2	t(4;5)(q21;q33)
SART3	t(5;12)(q33;q23)
SPECC1	t(5;17)(q33;p11)
TP53BP1	t(5;15)(q33;q22)
WDR48	t(3;5)(p21;q33)
X	t(1;5)(p22;q33)



- 22 patients, median age 49 years
- 15 different partners genes identified
- Eosinophilia absent in 21% of cases
- With imatinib, all reached a CHR. CMR was reached in 86% of pts after a median time of 19 months
- 5 pts in BP: 3 pts experience relapse after HSCT and 2 pts died with complex karyotype
- 5-year OS was 83% (most with low dose imatinib as maintenance)

- About 16 different partner genes identified. The most common is *ZMYM2* for t(8;13)(p11.1;q12.1)
- Median age late ‘30; male/female ratio 1.5:1
- Eosinophilia in about 70%. Commonly presenting with nodal T-ALL/LBL with MPN-like features or blast phase (myeloid, B-lymphoblastic or mixed). Different phases and lineages of the disease can be seen in the same patient.
- Organ involvement is not frequent
- Aggressive course. No response to imatinib. Clinical and cytogenetic responses to pemigatinib

- Bone marrow involvement with a chronic myeloid neoplasm, usually an MPN or MDS/MPN invariably with eosinophilia, neutrophilia, or monocytosis

OR

- Bone marrow involvement with blast phase, either B- or T-ALL, AML, or MPAL

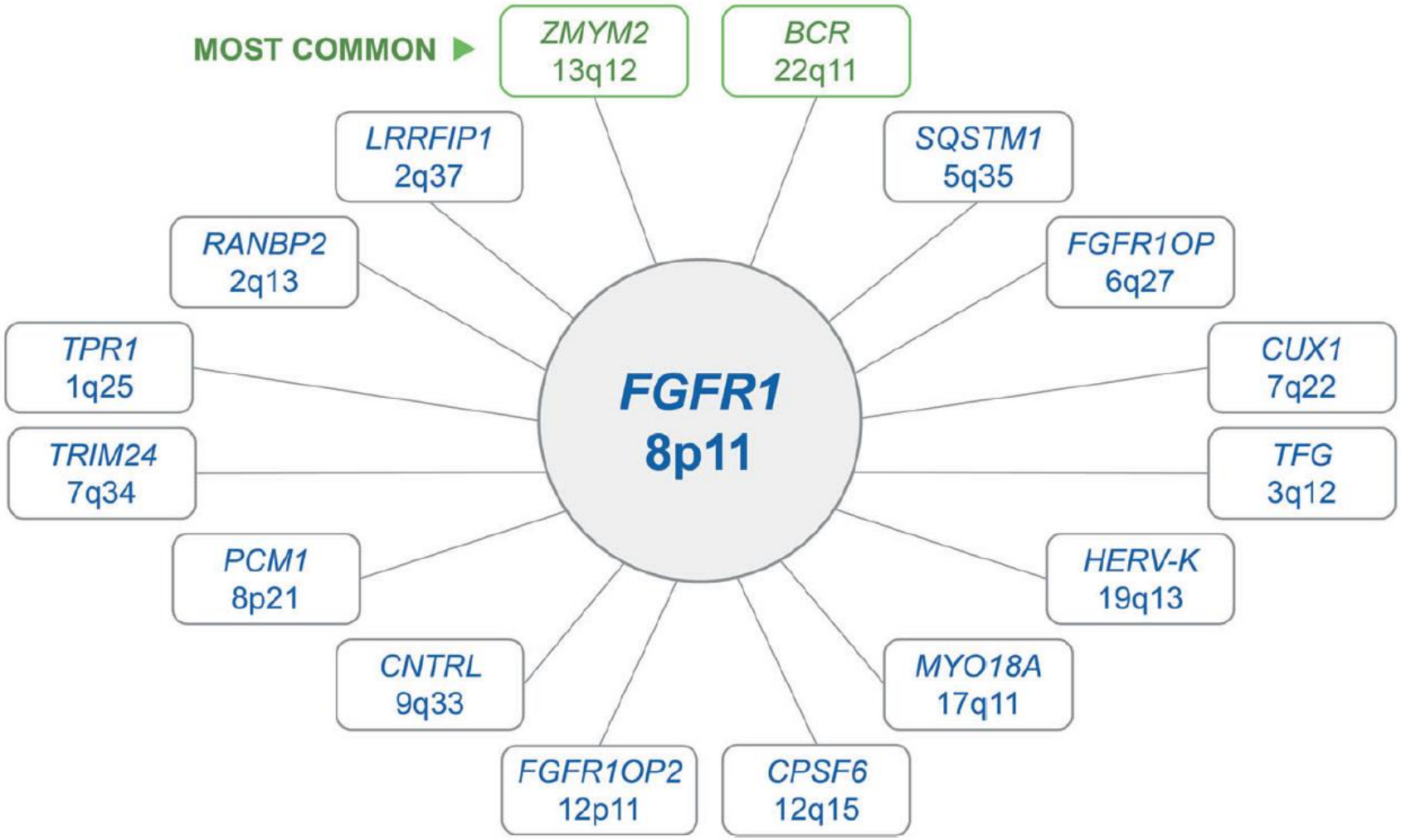
AND/OR

- Extramedullary involvement with a blast-phase, either B- or T-ALL, AML, or MPAL

AND

- Presence of t(8;13)(p11;q12) or variant 8p11 translocation leading to FGFR1 rearrangement in myeloid cells, lymphoblasts, or both.

FGFR1 positive M/L-eo TK: fusion partners

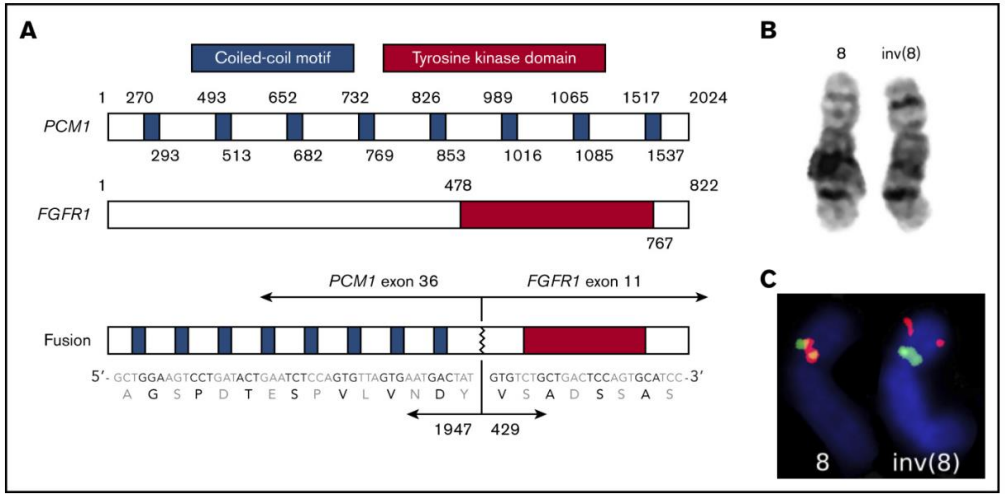


Shomali et al Leukemia 2023

Ponatinib limited efficacy in FGFR1 positive M/L-eo TK

- Seven consecutive FGFR1^{+} MLN-eo patients. Median age was 52 years (range, 48-74) with a male predominance (n=5). Median observation time after diagnosis was 10 months (range, 5-36).
- Only three patients [all with t(8;13)] had eosinophilia of >0.5 x 10^{9}/l.
- Bone marrow biopsy revealed a hypercellular marrow consistent with myeloproliferative neoplasm in all patients. Five patients presented with concomitantly diagnosed lymphoid neoplasms, i.e. T-lymphoblastic lymphoma (T-LBL, n=3), biclonal accelerated phase (n=1) or lymphoid blast phase of MPN/B-cell acute lymphoblastic leukemia (B-ALL, n=1).
- RT-PCR identified the associated fusion genes *ZMYM2::FGFR1* (n=3), *BCR::FGFR1* (n=3), and *FGFR1OP::FGFR1* (n=1), respectively.
- A temporary partial hematologic response (control of peripheral blood cell count) was observed in 6 of 7 patients.
- One patient with t(8;13) achieved a partial cytogenetic response.

- Futibatinib is a structurally novel, highly selective, and potent FGFR inhibitor, which binds covalently and irreversibly to a conserved cysteine residue in the FGFR kinase domain within the ATP-binding pocket.
- A single patient with *PCM1::FGFR1* fusion gene treated with the drug (20 mg/d) after prednisone: after 7 days complete absence of eosinophilia and onset of hyperphosphatemia
- Disappearance of *PCM1::FGFR1* after 175 days of treatment



Kasbekar et al Blood Adv 2020

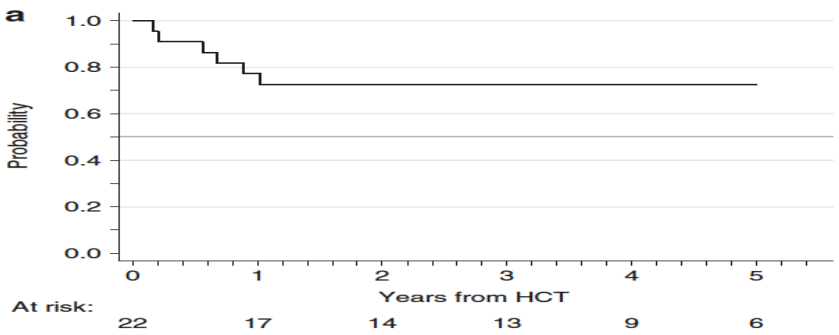
Pemigatinib in FGFR1 positive M/L-eo TK: FIGHT-203 trial

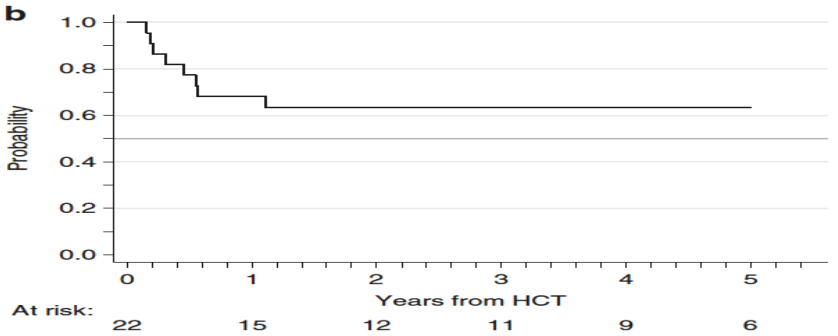
	CR, n (%)		CCyR, n (%)	
	Investigator	CRC	Investigator	CRC
Responses, N=31 for CR and N=33 for CCyR	20 (64.5)	24 (77.4)	24 (72.7)	25 (75.8)
CP disease only, N=18 (CP without EMD)	15 (83.3)	16 (88.9)	14 (77.8)	16 (88.9)
Any BP component, N=13 (BP with or without EMD; CP with EMD; EMD only)	5 (38.5)	8 (61.5)	8 (61.5)	7 (53.8)
Treated MLN with no morphologic evidence of disease but persistent cytogenetic abnormality, N=2	NE	NE	2 (100)	2 (100)

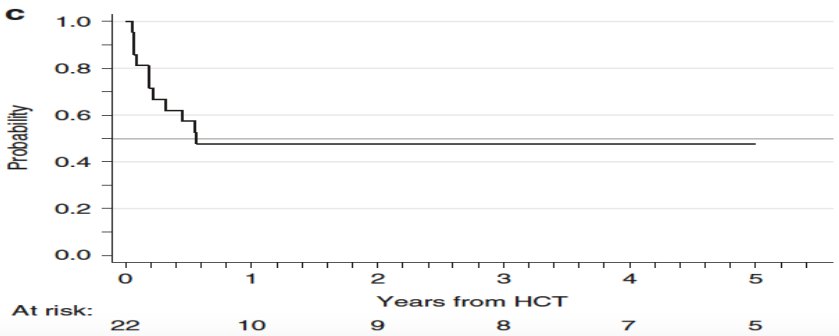
BP, blast phase; CCyR, complete cytogenetic response; CP, chronic phase; CR, complete response; CRC, central review committee; EMD, extramedullary disease; MLN, myeloproliferative neoplasm; NE, not evaluable.

- 34 pts enrolled and treated, median age 61 years, 59% were female
- Only 5 were treatment naïve and 3 have received HSCT
- Treatment ongoing in 18 pts (53%)
- Among the 31 pts with BM and/or EMD involvement, CR rates per investigator and CRC assessments were 64.5% and 77.4%, respectively. Among the 33 pts evaluable for CyR, CCyR rates were 72.7% and 75.8%, respectively. Median durations of CR have not been reached.

Allogeneic HSCT in FGFR1 positive M/L-eo TK







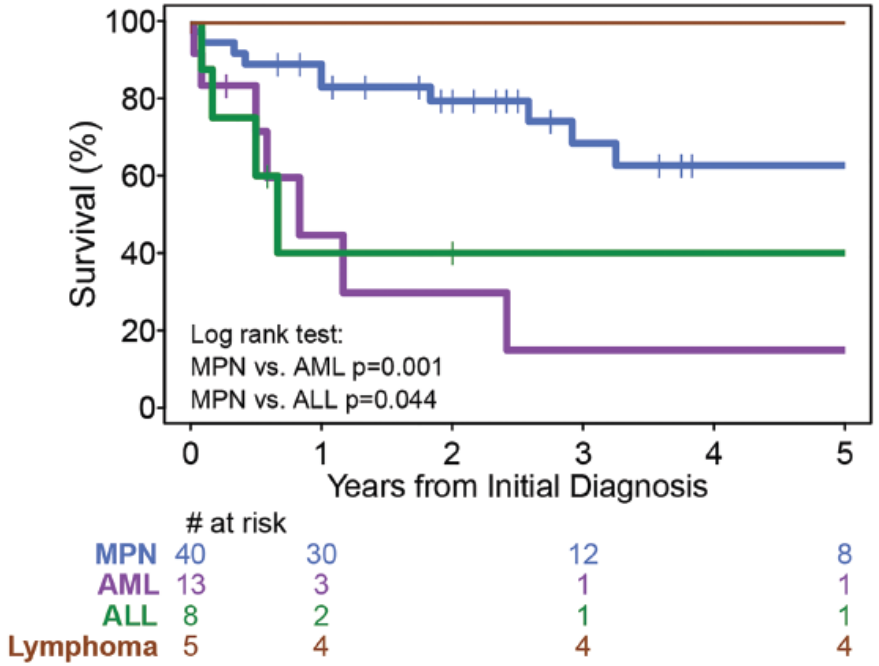
- 22 pts
- Distribution according to cytogenetic subtype was: t(8;13) in 11 cases, t(8;22) in 7 cases, t(6;8) in 2 cases, and other (n = 2).
- Over a third of patients displayed a chronic myeloproliferative (MPN) phenotype, another third showed MPN features with concomitant lymphoma or acute leukemia, and the remaining ones presented as acute leukemia.
- After a median follow-up of 4.1 years from transplant, the estimated 5-year OS, PFS, non-relapse mortality and relapse incidence was 74%, 63%, 14% and 23%, respectively.
- Two pts relapsed and achieved CR with ponatinib or pemigatinib (alive at 34.5 and 37 months from relapse, respectively).

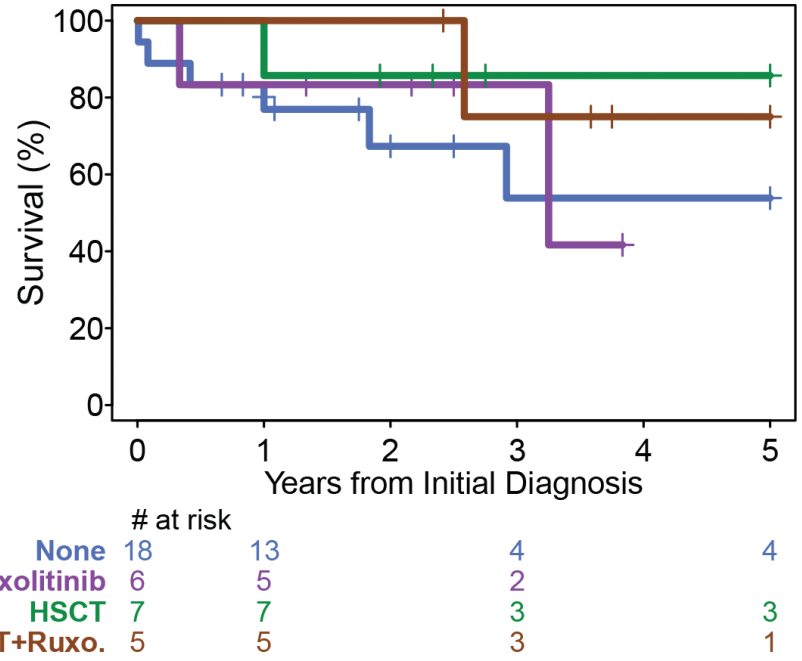
Hernandez-Boluda et al Bone marrow transpl 2022

- The *PCM1::JAK2* fusion gene arising from t(8;9)(p22;p24)
- JAK2 can also rearrange with ETV6 or BCR
- Somatic mutations are more similar to cases with rearranged PDGFRA or PDGFRB
- Male predominance
- Eosinophilia in more than 70% of cases with dysplastic erythroid proliferation. Indolent course in patients with myeloid proliferation; poor outcome in pts with blast phase.
- Ruxolitinib associated with short lived responses and limited benefits

Wang et al Am J Hematol 2023

PCM1::JAK2 positive: a series of 66 patients

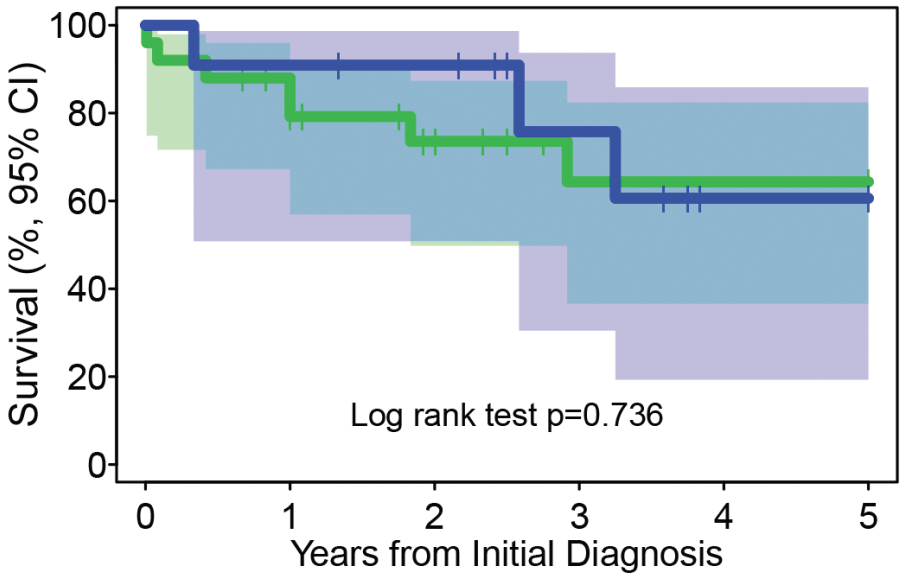




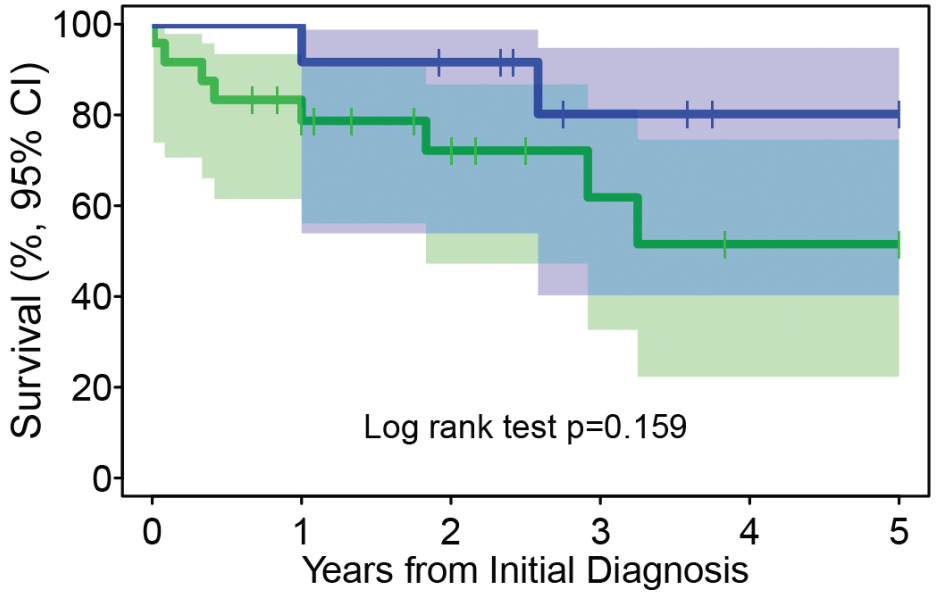
- 66 pts, median age 50 years, 77% male
- Diagnosis of MPN in 40, acute leukemia in 21 and T-cell cutaneous lymphoma in 5
- The 5-year survival for the MPN, AML, ALL, and lymphoma groups are 62.7, 14.9%, 40.0%, and 100%, respectively.

Kaplan et al Oncologist 2022

PCM1::JAK2 positive: a series of 66 patients (II)



# at risk				
No Ruxolitinib	25	20	7	7
Ruxolitinib	11	10	5	1



# at risk				
No HSCT	24	18	6	4
HSCT	12	12	6	4

- Too few patients have been treated with ruxolitinib to draw conclusions regarding its effect on survival while the 5-year survival for MPN patients with or without HSCT was 80.2% (40.3%-94.8%) versus 51.5% (22.3%-74.6%), respectively.
- The T-cell cutaneous lymphoma patients have all survived at least 7 years.

PCM1::JAK2 positive myeloid sarcoma

Reference	Age, yrs Sex	Type	Biopsy site	Initial diagnosis	Treatment	ASCT	Response	Survival (mths) (from diagnosis of MS to the last follow-up reported)
Rizzuto G, *et al.* 2022[6]	53 F	MS	Right ileo-psoas muscle	MF, B-ALL	Two cycles of FLAI regimen; a cycle of high-dose methotrexate and cytarabine, also for CNS prophylaxis; local radiotherapy; ASCT; ruxolitinib as post-transplant maintenance	ASCT after CR	CR	14
Luedke C, *et al.* 2020[5]	32 M	EBS	Axillary LN	Myeloid neoplasm	NA	NA	NA	NA
Song I, *et al.* 2016[7]	42 M	MS	Right axillary LN and an inguinal LN	MPN-U	Chemotherapy with arabino-side and erythromycin	Awaiting	Unknown	3

- Single case and review of all MS reported. A 72 year old pt with MF + eosinophilia (RUNX1 8%)
- Erythroid blastic involvement of a lymphnode

Zhange et al Haematologica 2023

- About 30 cases described
- Male predominance (ratio 2.2:1), median age late ’40
- Rearrangements largely detectable by cytogenetics (chromosome 13q12), but can be cryptic
- Frequent eosinophilia in blood (70-80%), bone marrow (MPN with eosinophilia, or MPN/MDS similar to CMML or aCML) and tissue, but extramedullary localization are quite common. Commonly presented as T-ALL/LBL or myeloid sarcoma with CEL-, MPN- or MDS/MPN-like BM features.
- Aggressive clinical course. Allogeneic transplant is need.

Wang et al Am J Hematol 2023

M/L-eo with FlT3 rearrangements case series

	Case	Sex/ age	Organomegaly/ lymphadenopathy	Bone marrow diagnosis	Extramedullary lesions	Peripheral blood findings						Treatments	FU	
						WBC ($x10^9$/L)	HGB (g/dL)	PLT ($x10^9$/L)	Eos (%)	Mono (%)	Blasts (%)		Time (mon)	A/D
ETV6	1	F/38	No/Yes	MPN-unclassifiable	T-ALL (LN)	23.4	13.7	308	3	11	0	Chemo, HSCT	15	Died
	2	M/30	No/Yes, multiple	Normal BM	MPAL, T/B (LN)	5.3	14.7	178	7.4[a]	NA	0	Chemo, HSCT	34	ACR
	3	M/60	No/No	Normal BM	Myeloid sarcoma	7	14.9	204	1	9	0	Radiation, Chemo, sunitinib, then Sorafenib	14	ACR
	4	F/43	Splenomegaly/Yes, multiple	CMML-2	T-cell lymphoma (4 months later)	46.7	8.3	85	5	41	7	Azacitidine, ruxolitinib, HSCT	50	ACR
	5	F/41	No/No	CEL, NOS	None	20	10.3	90	14	3	0	Sorafenib, HSCT	85	ACR
	6	M/75	No/No	MDS-EB-2→AML (4 months later)	None	4.5	8.4	40	13	5	5	Decitabine, venetoclax	5	Died
	7	M/2	Yes/Yes, multiple	T-ALL, ETP → MPAL, M/T	T-ALL, ETP (LN)	21.6	12.1	41	0[a]	10	14	Chemo, SCT	152	ACR
	8	M/43	No/No	CEL, NOS	Myeloid sarcoma (29 months later)	23.5	14.6	302	9	0	0	CLIA + gilteritinib	30	AWD
	9	M/20	NA/NA	CEL, NOS with aberrant mast cells	Myeloid sarcoma	6.5	13.6	252	22	6	8	Chemo, SCT	28	Died
	10	F/72	No/No	T-ALL	None	78.8	8.0	208	3	3	24	miniCVD, venetolax	21	Died
	11	M/80	No/No	MDS-EB-2	None	3.1	9.7	33	4	7	11	Decitabine, mylotarg	2	Died
	12	F/55	Yes/No	CMML-2→AML	None	54.3	14.1	19	0	29	6	Cytarabine	16	Died

Heterogenous presentation.

6 cases with ETV6, 7 with extramedullary involvement, 67% with eosinophilia 50% with somatic mutations

Tang et al Modern Pathol 2021

M/L-eo with FlT3 rearrangements: review series

Reference	Sex/age	t(13q12;v)	Partner gene	Diagnosis (BM)	Diagnosis (EM)	Eos	Molecular mutation	Treatment	FU and outcome
Chao (2020)	M/20 W	t(13;14)(q12;q32)	*CCDC88C*	JMML	No	No	No JMML associated	Failed high dose chemo, then Sorafenib, prior to and post SCT maintenance	~1 year, ACR
Chonabayashi (2014)	M/33	t(12;13)(p13;q12)	*ETV6*	MPN-eo	T-ALL (LN)	Yes	NA	hyperCVAD, SCT	>6 years, ACR
Chung (2017)	M/62	t(13;14)(q12;q32)	*TRIP11*	MPN-eo, SM	T-ALL (LN) two-month later	Yes	*KIT* D816V	Hydroxyurea	4 month, died
Grand (2007)	F/32	t(2;13;2;21) (p13;q12;q33;q11.2)	*SPTBN1*	aCML	No	Yes	NA	SCT, donor lymphocyte infusion.	12 years, ACR
Hosseini (2014)	F/38	t(12;13)(p13;q12)	*ETV6*	MPN-eo	T/myeloid MPAL	Yes	NA	HyperCVAD, SCT	23 month, died
Jawhar (2017)	F/48	NA (cryptic)	*ZMYM2*	MPN-eo AML (10-mon later)	No	Yes	28-gene NGS, all negative	chemo, SCT	19 month, died
Jawhar (2017)	M/47	NA (cryptic)	*ZMYM2*	MPN-eo	No	Yes	*KIT* and *JAK2* negative	Sunitinib monotherapy	10 month, ACR
Munthe-Kaas (2020)	M/3.5	NA (cryptic)	*ZMYM2*	Leukocytosis with eosinophilia	T-ALL (LN)	Yes	NA	Chemo, Sorafenib monotherapy for relapse	43 month, ACR
Shao (2020)	M/52	t(13;14)(q12;q32)	*TRIP11*?	MPN-eo, 5% T-ALL	T-ALL (LN)	Yes	54-gene NGS, all negative	hyperCVAD, then Sorafenib monotherapy at disease progression	9 month, died
Troadec (2017)	F/71	t(3;13)(q13;q12)	*GOLGB1*	*MPN-eo*	T-ALL (LN)	Yes	NA	CHOP	3 month, died
Tzankov (2008)	M/46	t(13;13)(q12;q22)	unknown	MPN with SM B-ALL (4-mon later)	No	Yes	*KIT* D816V	Chemo, SCT	13 years, ACR
Vu (2006)	F/68	t(12;13)(p13;q12)	*ETV6*	MPN-eo	No	Yes	NA	Hydroxyurea, imatinib	21 month, died
Walz (2011)	M/60	t(12;13)(p13;q12) in complex karyotype	*ETV6*	MPN-eo in accelerated phase	T cell lymphoma (LN)	Yes	NA	Sunitinib, sorafenib, then chemo	8 month, died
Walz (2011)	M/29	t(12;13)(p13;q12)	*ETV6*	MPN-eo	T-ALL (LN)	Yes	NA	CHOP, hyperCVAD, SCT, sunitinib	? month, died
Zhang (2018)	M/49	t(12;13)(p13;q12)	*ETV6*	CMML-1	Myeloid sarcoma	Yes	NA	CALG-M, SCT	43 month, ACR
Zhang (2018)	M/47	t(13;17)(q12;q12)	*MYO18A*	aCML	Myeloid sarcoma 1-year later	Yes	35-gene NGS, all negative	hydroxyurea, ruxolitinib, SCT	1 year, died

Heterogenous partner genes. ETV6 presented as chronic diseases

6 pts treated with TKIs: 3 alive in CR.

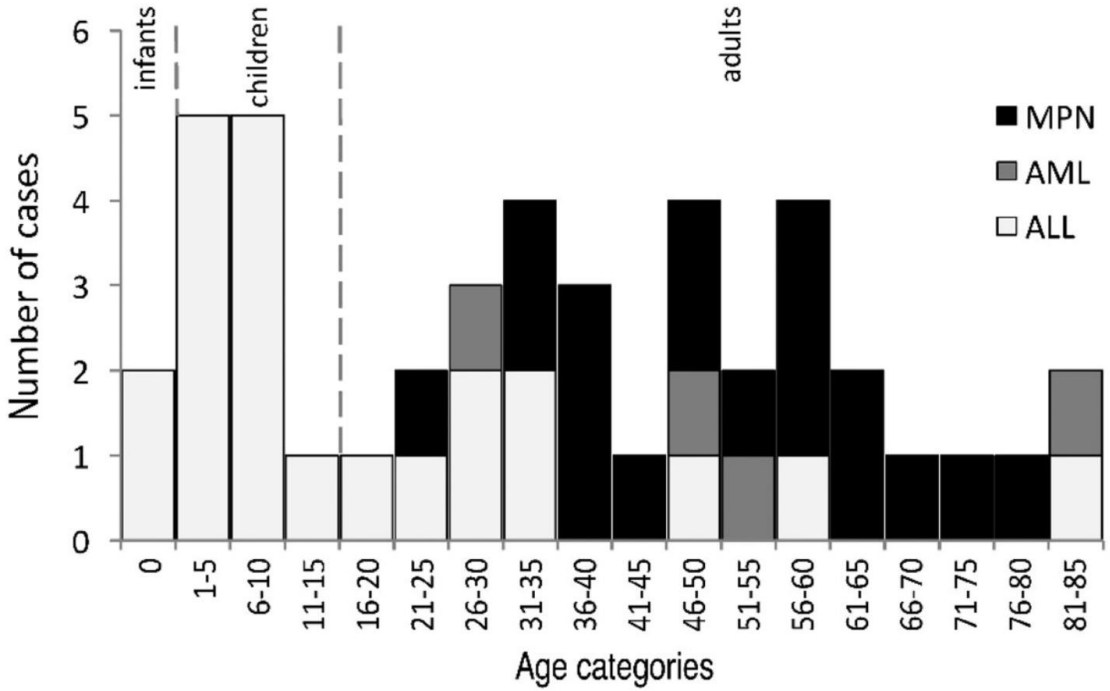
Tang et al Modern Pathol 2021

M/L-eo TK with *ETV6::ABL1*: baseline features

- *ABL1* gene, located on 9q34.12 encodes a tyrosine kinase protein that plays a role in the regulation of apoptosis and cell proliferation
- Male to female ratio 3:1. Median age late ‘40s
- Reported in MPN, ALL (B or T), AML. Eosinophilia 90%
- 13 partners described, most produced by insertion or either *ABL1* in *ETV6* or *ETV6* in *ABL1*
- CML-like morphology, with eosinophilia and basophilia, with possible blast crisis

Wang et al Am J Hematol 2023;
Morales-Camacho et al Cancers

M/L-eo TK with *ETV6::ABL1*: case series



Diagnosis	Age group	Male	Female	Total
ALL	*infant*	*1*	*1*	*2*
	childhood	*6*	*5*	*11*
	adult	*5*	*4*	*9*
		12	**10**	**22**
AML		**4**	**0**	**4**
MPN		**12**	**5**	**18***
Total		28	15	44

- 44 cases of *ETV6::ABL1*-positive [22 cases of ALL (13 children, 9 adults) and 22 myeloid malignancies (18 MPN, 4 AML)]
- ALL *ETV6::ABL1* is rare in childhood (0.17% cases) and slightly more common in adults (0.38%)
- In adulthood *ETV6::ABL1* is more common in *BCR-ABL1*-negative CML-like myeloproliferations than in ALL
- The genomic profile of *ETV6::ABL1* ALL resembled that of *BCR-ABL1* and *BCR-ABL1*-like cases with 80% of patients having concurrent *CDKN2A/B* and *IKZF1* deletions
- Over 60% of patients died, irrespectively of the disease or age subgroup examined

M/L-eo TK with other rare TK gene fusions

- Not yet included in the WHO
- Included some rearrangements like
  ETV6::FGFR2,
  ETV6::LYN
  ETV6::NTRK3
  BCR::RET
  RANBP2::ALK
- In some instances, treatment with TKIs could be feasible

Wang et al Am J Hematol 2023;
Morales-Camacho et al Cancers

1. Rare disorders
2. Usually male predominance
3. Heterogeneous presentation (MPN or AML/ALL +/- EMD)
4. Cytogenetic and molecular analysis needed for specific diagnosis
5. Some forms are extremely sensitive to TKI (imatinib)
6. Some other need intensive treatments and HSCT