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RESEARCH ARTICLE

Response to tyrosine kinase inhibitors in myeloid neoplasms associated with *PCM1-JAK2*, *BCR-JAK2* and *ETV6-ABL1* fusion genes

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Abstract

We report on 18 patients with myeloid neoplasms and associated tyrosine kinase (TK) fusion genes on treatment with the TK inhibitors (TKI) ruxolitinib (*PCM1-JAK2*, n = 8; *BCR-JAK2*, n = 1) and imatinib, nilotinib or dasatinib (*ETV6-ABL1*, n = 9). On ruxolitinib (median 24 months, range 2-36 months), a complete hematologic response (CHR) and complete cytogenetic response (CCR) was achieved by five of nine and two of nine patients, respectively. However, ruxolitinib was stopped in eight of nine patients because of primary resistance (n = 3), progression (n = 3) or planned allogeneic stem cell transplantation (allo SCT, n = 2). At a median of 36 months (range

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4-78 months) from diagnosis, five of nine patients are alive: four of six patients after allo SCT and one patient who remains on ruxolitinib. In *ETV6-ABL1* positive patients, a durable CHR was achieved by four of nine patients (imatinib with one of five, nilotinib with two of three, dasatinib with one of one). Because of inadequate efficacy (lack of hematological and/or cytogenetic/molecular response), six of nine patients (imatinib, n = 5; nilotinib, n = 1) were switched to nilotinib or dasatinib. At a median of 23 months (range 3-60 months) from diagnosis, five of nine patients are in CCR or complete molecular response (nilotinib, n = 2; dasatinib, n = 2; allo SCT, n = 1) while two of nine patients have died. We conclude that (a) responses on ruxolitinib may only be transient in the majority of *JAK2* fusion gene positive patients with allo SCT being an important early treatment option, and (b) nilotinib or dasatinib may be more effective than imatinib to induce durable complete remissions in *ETV6-ABL1* positive patients.

1 | INTRODUCTION

More than 70 different tyrosine kinase (TK) fusion genes with recurrent involvement of at least 6 TK genes (*PDGFRA*, *PDGFRB*, *FGFR1*, *JAK2*, *ABL1*, *FLT3*) have been identified in clinically and morphologically distinct myeloid neoplasms with or without eosinophilia.[1] Patients may present in chronic phase (CP) or blast phase (BP) of myeloid or lymphoid origin.[2] The WHO 2017 classification defines some but not all of these fusions within a distinct subgroup as "myeloid/lymphoid neoplasms with eosinophilia and rearrangement of *PDGFRA*, *PDGFRB*, *FGFR1* or *PCM1-JAK2* fusion gene" (MLN-eo).[3] Targeted treatment with TK inhibitors (TKI) is highly effective in many cases with rapid and durable complete remissions in patients with *PDGFR* fusion genes, for example, *FIP1L1-PDGFRA* or *ETV6-PDGFRB*.[4-7] In contrast, patients with fusions involving other TK, for example, *FGFR1* or *JAK2*, present with a more aggressive phenotype and a highly variable sensitivity to currently available TKI.[1,8-10] Long-term disease-free survival may therefore only be achieved through allogeneic stem cell transplantation (allo SCT).

To date, the disease characteristics and clinical course of approximately 40 *PCM1-JAK2* or *BCR-JAK2* positive patients, formed as a consequence of the reciprocal translocations t(8;9)(p22;p24) and t(9;22)(p24;q11), respectively, have been reported.[11] However, there are only a few reports upon treatment and potential responses to ruxolitinib.[9,12-15]

The *ETV6-ABL1* fusion gene may be difficult to recognize as it results from cytogenetically cryptic inversions, insertions or complex rearrangements involving chromosomal band 12p13 and 9q34. It is most frequently identified in infants and children with acute lymphoblastic leukemia (ALL, incidence <0.5%). Beside ALL, the phenotype may resemble in adults a myeloid neoplasm such as atypical chronic myeloid leukemia (aCML), chronic eosinophilic leukemia (CEL), myelodysplastic/myeloproliferative neoplasm unclassified (MDS/MPN-U) or MPN-U which are diagnosed in CP or BP. However, data on treatment and response to ABL1 inhibitors such as imatinib, nilotinib or dasatinib are limited to case reports or small cases series.[16-27]

We therefore sought to evaluate the clinical characteristics and response to various TKI in 18 patients with myeloid neoplasms and associated *PCM1-JAK2*, *BCR-JAK2* or *ETV6-ABL1* fusion genes. In an extended analysis, we integrated our data into the reports of 40 patients with *JAK2* fusion genes (*PCM1-JAK2*, n = 28)[8,9,12-15,28-40] or *BCR-JAK2* (n = 12)[41-52] and 14 patients with TKI-treated *ETV6-ABL1* positive chronic myeloid neoplasms.[16-27,53,54] This analysis provides a comprehensive overview of responses to TKIs in patients with these rare fusions.

2 | MATERIALS AND METHODS

2.1 | Patients

Eighteen patients with *PCM1-JAK2* (n = 8), *BCR-JAK2* (n = 1) [patients 6 and 7 were previously published,[9]] and *ETV6-ABL1* (n = 9) fusion genes were identified within the "German Registry for Disorders of Eosinophils and Mast Cells "and in cooperation with hematology centers in the UK (n = 3), Switzerland (n = 1) and USA (n = 1). All patients were treated with one or more TKIs for at least part of their clinical course. Patient demographics, disease characteristics, therapies, responses and follow-up data were collected. Data collection was compliant with the Declaration of Helsinki and approved by the ethics committee of the Medical Faculty Mannheim at the University Heidelberg, Germany. For supplementary analyses (eg, overall survival [OS], prognosis, impact of distinct treatment modalities), 40 patients with the *JAK2* fusion gene (*PCM1-JAK2*, n = 28; *BCR-JAK2*, n = 12) (all >18 years) and 14 patients with a TKI-treated *ETV6-ABL1* positive myeloid neoplasm and sufficient follow-up data were included from the literature.

2.2 | Cytogenetic and molecular analysis

Cytogenetic analysis and fluorescence in situ hybridization (FISH) were performed on bone marrow (BM) according to standard

procedures. Specific nested reverse transcription polymerase chain reaction (RT-PCR) was performed for confirmation of *PCM1-JAK2*, *BCR-JAK2* and *ETV6-ABL1* fusion transcripts[8,19,55] and for detection of residual disease. Complete cytogenetic response (CCR) was defined by a normal karyotype and complete molecular response (CMR) was defined by an undetectable fusion transcript by nested RT-PCR.

2.3 | Statistical analyses

All clinical and laboratory parameters are expressed as median and range. The OS was determined from date of diagnosis and calculated by using the Kaplan-Meier method and compared using the log-rank test. All statistical analyses were performed using GraphPad Prism Software, Inc. version 7.

3 | RESULTS

3.1 | Disease characteristics of patients with *JAK2* fusion genes

At diagnosis, the median age of the nine patients (1-9) was 63 years (range 29-73 years), eight of nine patients were male. Seven patients presented in CP, and two patients in primary BP (myeloid BP/AML, n = 1; lymphoid BP/ALL, n = 1). Notable clinical and morphological characteristics included: leukocytosis (nine of nine patients, median 29×10^9/L, range 10-55), eosinophilia ≥1.5×10^9/L in three of eight (38%) patients with eosinophils between 0.5 and 1.5×10^9/L in two of eight patients (25%), splenomegaly (six of eight patients, 75%), hypercellular BM (seven of eight patients, 87%) with left-shifted granulopoiesis (seven of eight patients, 87%), dysplastic erythropoiesis with giant immature erythrons (six of eight patients, 75%), eosinophilia (five of eight patients, 62%) and fibrosis (seven of eight patients, 87%). Initial histomorphological diagnoses prior to identification of the *JAK2* fusions were MDS/MPN-U (n = 5, including the *BCR-JAK2* positive patient), CML-like MPN-U (n = 2), myeloid BP/AML (n = 1) and lymphoid BP/ALL (n = 1) (Table 1). Cytogenetic analyses revealed a t(8;9)(p22;p24) in six patients, a t(8;9)(p22;p24),+6,+8,+22, a t(8;9;9)(p22;p24;p13), and a t(9;18)(p24;q12),t(14;18)(q21;q23) in one patient each. In the latter patient, a *BCR-JAK2* fusion was identified by RNAseq analysis.[9]

3.2 | Treatment of patients with *JAK2* fusion genes

All patients received monotherapy with ruxolitinib as first line treatment. Analogous to treatment in myelofibrosis, the initial dose was chosen according to platelets and adjusted to hematological toxicity. The last administered doses were 5 mg BID (patients no. 2, 4, 7), 15 mg BID (patient no. 9) and 20 mg BID (patients no. 1, 3, 5, 6, 8). After median 4 months (range 2-18 months), five of nine patients (no. 2, 3, 5, 6, 7) achieved a complete hematological response (CHR) on ruxolitinib (median treatment duration 24 months; range 2-36 months). Complete cytogenetic response (CCR, patient no. 7) or complete molecular response (CMR, patient no. 6) was observed in one patient each. Patient no. 1 developed a fatal myeloid BP within 1 month on ruxolitinib. Patient no. 2 is in complete CHR on ruxolitinib for 26 months (Figure 1A). Patient no. 8 was treated with azacitidine after primary resistance to ruxolitinib but finally died because of progressive disease. Five patients (no. 3, 4, 5, 6, 7) underwent allo SCT because of progressive disease (n = 1; patient no. 3), cytogenetic relapse/clonal evolution (n = 2; patients no. 5, 7) or planned allo SCT (n = 2; patients no. 4, 6) after a median of 26 months (range 2-38 months) on ruxolitinib. After allo SCT, four of six patients (no. 3, 4, 6, 7) are disease-free for a median of 40 months (range 5-46 months) while two of six patients died. Patient no. 5 developed a high-grade Burkitt-like B-cell lymphoma in the BM with a complex karyotype including a t(8;9)(p22;p24), a rearrangement of *JAK2* by FISH analysis and a *PCM1-JAK2* fusion gene by RT-PCR. This indicated a relapse in terms of a lymphoid BP and patient no. 5 died at month +5 after allo SCT. Patient no. 9 with an initial diagnosis of BP died because of relapse which was also ruxolitinib-resistant at month +6. Patient no. 4 developed a *PCM1-JAK2* negative early stage Hodgkin's lymphoma at month +43 while in CCR and achieved a complete remission on chemotherapy. Median 36 months (range 4-78 months) from diagnosis, five of nine patients are alive after allo SCT (n = 4) or on ruxolitinib only (n = 1), respectively (Figure 1A).

3.3 | Inclusion of *PCM1-JAK2* and *BCR-JAK2* positive patients from the literature

The median age of the 49 patients with *JAK2* fusion genes was 50 years (range 22-84 years) with a marked male predominance (39/49, 80%). Overall, 17 of49 (35%) patients were diagnosed with primary BP (n = 11; myeloid BP/AML, n = 7; lymphoid BP/ALL; n = 4) or progressed to secondary BP (n = 6; myeloid, n = 5; lymphoid, n = 1) at a median of 20 months (range 7-72 months) from diagnosis.[8,14,41,50] Treatment with ruxolitinib for 16, 26 and 46 months, respectively, has only been reported in three further patients who achieved CHR (n = 3) or CCR (n = 2).[12-15] After a median follow-up of 12 months (range 0-204 months), 21/49 (43%) patients died. The OS was significantly different between CP and BP (90.0 months, range 0-204 months, vs 18.2 months, range 0-180 months, P = .03). With censoring for allo SCT, OS was not different for patients treated with or without ruxolitinib (Figure 2). An allo SCT was performed in 18/49 (37%) patients.[8,31-33,36-38,42,46,49,50,52,56] Two further patients underwent an autologous SCT (auto SCT) after intensive chemotherapy for ALL.[33,56] When both transplant cohorts were combined, the median survival was significantly improved compared to not transplanted patients (median not reached, range 0-204 months, vs 22 months, range 3-78 months; P = .02).

TABLE 1 Clinical characteristics of 18 patients with *PCM1-JAK2* (n = 8, no. 1-5 and 7-9), *BCR-JAK2* (n = 1, no. 6) and *ETV6-ABL1* (n = 9, no. 10-18) fusion gene

No.	Male (M)/ fe-male (F)	Age at diag-nosis (y)	Karyotype	Fusion gene	WBC $\times 10^9$/L	Eos $\times 10^9$/L, (%)	Plt/nL	Spleno-megaly (yes, 1; no, 0)	Bone marrow	Phase	Diagnosis	Months after diagnosis	Outcome alive, 0; death 1
1	M	76	t(8;9)(p22;p24)	*PCM1-JAK2*	28.7	1.43 (5)	126	0	Left-shifted GP ↑, dysplastic EP↓, Eo↑, MP↓, MC↑, MFII°	CP	CML-like, MPN	4	1
2	M	70	t(8;9)(p22;p24)	*PCM1-JAK2*	29.8	0.30 (1)	118	1	Left-shifted GP ↑, dysplastic EP↑[a], Eo↑, MP↓, MC↑, MFI°	CP	MDS/MPN, aCML	34	0
3	M	49	t(8;9;9)(p22;p24;p13)	*PCM1-JAK2*	25.6	n.a.	96	1	Left-shifted GP ↑, dysplastic EP↑[a], Eo n, MP ↓, MC↑, MFII°	CP	MDS/MPN	46	0
4	M	29	t(8;9)(p22;p24)	*PCM1-JAK2*	21.7	2.38 (11)	67	1	no BM histology	CP	CML-like MPN	53	0
5	M	50	t(8;9)(p22;p24	*PCM1-JAK2*	12.7	1.65 (13)	263	1	Left-shifted GP ↑, dysplastic EP↑[a], Eo↑, MP↓, MC↑, MFII°	CP	MDS/MPN	36	1
6	M	69	t(9;18)(p24;q12),t(14;18)(q21;q23)	*BCR-JAK2*	36.6	1.10 (3)	1254	1	Left-shifted GP ↑, dysplastic EP↑[a], Eo↑, dysplastic MP, MC n, MFII°	CP	MDS/MPN-eo	78	0
7	M	51	t(8;9)(p22;p24)	*PCM1-JAK2*	48.8	2.44 (5)	70	1	Left-shifted GP ↑, dysplastic EP↑[a], Eo↑, blasts 10%, dysplastic MP, MC?, MFI°	AP	MDS/MPN	78	0
8	F	69	+6,+8,t(8;9)(p22;p24),+22	*PCM1-JAK2*	10.5	0.10 (1)	236	0	MFIII° osteosclerosis, [b] blasts 20%	BP	AML-M4	15	1
9	M	63	t(8;9)(p22;p24)	*PCM1-JAK2*	55.2	no	57	0	Sheets of blasts, no MF	BP	Pre-B-ALL	18	1
10	M	54	46,XY,der(12)t(12;13)(p11;21),der(13)t(12;13)(p11;q14).ish ins(12;9)(p13;q34q34)(ABL+,ETV6+;ABL+,ETV6-)[17]/46,XY [3]	*ETV6-ABL1*	143.0	7.15 (5)	165	1	Hypercellular, GP ↑, dysgranulopiesis, Eo↑, MC↑, MF no	CP	aCML	40	0
11	M	20	46,XY t(9;12)(q34;p13) [10]	*ETV6-ABL1*	85.5	5.64 (7)	73	1	Hypercellular, GP ↑, dysgranulopoiesis, Eo n, MC n, MF I°	CP	aCML	20	0
12	M	61	46, XY,del(6)(p11 p25),der(9)t(9;12)(q34;p13,der(12)ins(12;6)(q12;p11p21) [11/]46XY,del(6)(p11p25),der(9)t(9;12)(q34;p13),(der(12)(6pter- > 6q21::12p13- > 12q12::6p11- > 6p21::12q12- > 12qter)	*ETV6-ABL1*	38.6	6.56 (17)	878	n.a.	Hypercellular, GP ↑, Eo ↑, MC ↑, MF I°	CP	MDS/MPN (CMML)	15	0
13	M	30	46,XY [20]	*ETV6-ABL1*	20.9	2.00 (10)	301	0	Hypercellular, GP ↑, Eo ↑, MC n, MF n.a	CP	MPN-eo	20	1
14	F	46	46,XX,t(9;12)(q34;p13)	*ETV6-ABL1*	83.7	2.50 (3)	591	1	Hypercellular, GP ↑, Eo ↑, MC n, MF II-III°	CP	aCML	58	0

TABLE 1 (Continued)

No.	Male (M)/ fe-male (F)	Age at diag-nosis (y)	Karyotype	Fusion gene	WBC $\times 10^9$/L	Eos $\times 10^9$/L, (%)	Plt/nL	Spleno-megaly (yes, 1; no, 0)	Bone marrow	Phase	Diagnosis	Months after diagnosis	Outcome alive, 0; death 1
15	M	61	46, XY,ins(12;9)(p12;q34q22) [20]	*ETV6-ABL1*	n.a.	(17)	n.a.	n.a.	Hypercellular, GP ↑, Eo ↑, MC n, MF I-II°	CP	MPN-eo	57	0
16	M	68	12p13 aberration	*ETV6-ABL1*	3.9	increased	n.a.	n.a.	Blasts, Eo n, dysplastic EP, MF II°	BP	sAML (from MDS)	3	0
17	M	29	47,XY,del(1)(q21),+8,der(16)t(1;16)(q21;q24) [10]	*ETV6-ABL1*	62	6.20 (10)	16	1	Blasts 60%, Eo ↑, MC 20%, MF II°	BP	AML (monocytic)	4	0
18	F	53	46,XX t(9;12)(q34;p13)	*ETV6-ABL1*	n.a.	7.00	n.a.	n.a.	GP ↑, Eo↑,MF n.a.	BP	BM: MPN-eo; Ln: T-LBL	23	1

Abbreviations: BP, blast phase; BM, bone marrow; CP, chronic phase; Eos, eosinophils; EP, erythropoiesis; GP, granulopoiesis; Ln, lymph node; MP, megakaryopoiesis; MC, mast cells; MDS/MPN, myelodysplastic/myeloproliferative neoplasm; MF, myelofibrosis; n.a., not available; Plt, platelets; sAML, secondary AML; ↑, increased; ↓, decreased.

[a]Giant erythroblastic erythrons.

[b]No further morphological assessment possible.

3.4 | Disease characteristics of patients with an *ETV6-ABL1* fusion gene

At diagnosis, median age (n = 9, patients no. 10-18) was 46 years (range 20-68 years); seven of nine patients were male. Six patients presented in CP, three patients in BP (myeloid/AML, n = 2; T-lymphoblastic lymphoma, n = 1). Relevant clinical and morphological characteristics included: left-shifted leukocytosis (six of seven patients; median 84×10^9/L, range, 21-143 $\times 10^9$/L), eosinophilia ≥1.5 $\times 10^9$/L in nine of nine patients (median 6.1 $\times 10^9$/L, range 2.0-7.1 $\times 10^9$/L), splenomegaly (four of five patients), hypercellular BM (nine of nine patients) and fibrosis (six of seven patients) (Table 1). In CP, histomorphological diagnoses included aCML (n = 3), chronic eosinophilic leukemia (CEL, n = 2) and MDS/MPN-U (n = 1). The 3 BP patients were diagnosed with myeloid BP/AML (n = 2) or CEL and concomitant T-cell lymphoblastic lymphoma (T-LBL, n = 1). Cytogenetic analyses revealed a t(9;12)(q34;p13) in four patients, a complex karyotype in three patients, an ins(12;9)(p13;q34q22) and a normal karyotype in one patient each. In all cases, the *ETV6-ABL1* fusion was confirmed by FISH analysis and/or RT-PCR.

3.5 | Clinical course of *ETV6-ABL1* positive patients

At a median of 3 months (range 0-6 months) from diagnosis, all nine patients were treated with a TKI (imatinib, n = 5; nilotinib, n = 3; dasatinib, n = 1) at standard doses. Prior to treatment with the various TKIs, five patients were treated with hydroxyurea (patients no. 10, 11, 12, 15, 18), one patient with hydroxyurea and cytarabine (patient no. 17) and one patient with intensive chemotherapy (patient no. 16). Two patients were primarily treated with a TKI (patients 13, 14). On imatinib (n = 5, patients no. 12-15, and 18), three of five patients (patients 12, 13, 14) achieved a CHR within 3 months which was rapidly lost in two patients after 5 (patient no. 14) and 9 (patient no. 13) months, respectively. Patient no. 12 did not achieve a CCR on imatinib. He was switched to nilotinib, achieved a CCR at month 3 and underwent an allo SCT. Patient 13 developed a myeloid sarcoma. After local radiation, he received an allo SCT but died 8 months later due to GvHD while in CMR. Patient no. 14 switched to nilotinib and achieved a CCR and CMR after 3 and 10 months, respectively. Patient 15 showed progressive disease on imatinib after 2 months. He was switched to dasatinib and achieved CHR, CCR and finally CMR after 14 months. Patient 18 presented with concurrent diagnosis of CEL and T-LBL. There was only a partial clinical/hematological response on imatinib (8 months), dasatinib (9 months) and nilotinib (2 months), and the patient died 23 months after diagnosis, because of progression to myeloid BP/AML. One patient (no. 16) with secondary AML was initially treated with intensive chemotherapy. Due to persistence of blasts, nilotinib was initiated but switched to dasatinib after 2 months due to lack of efficacy. The other patient (no. 17) received nilotinib as bridging treatment to allo SCT but developed leptomeningeal involvement in otherwise ongoing CHR after 3 months.

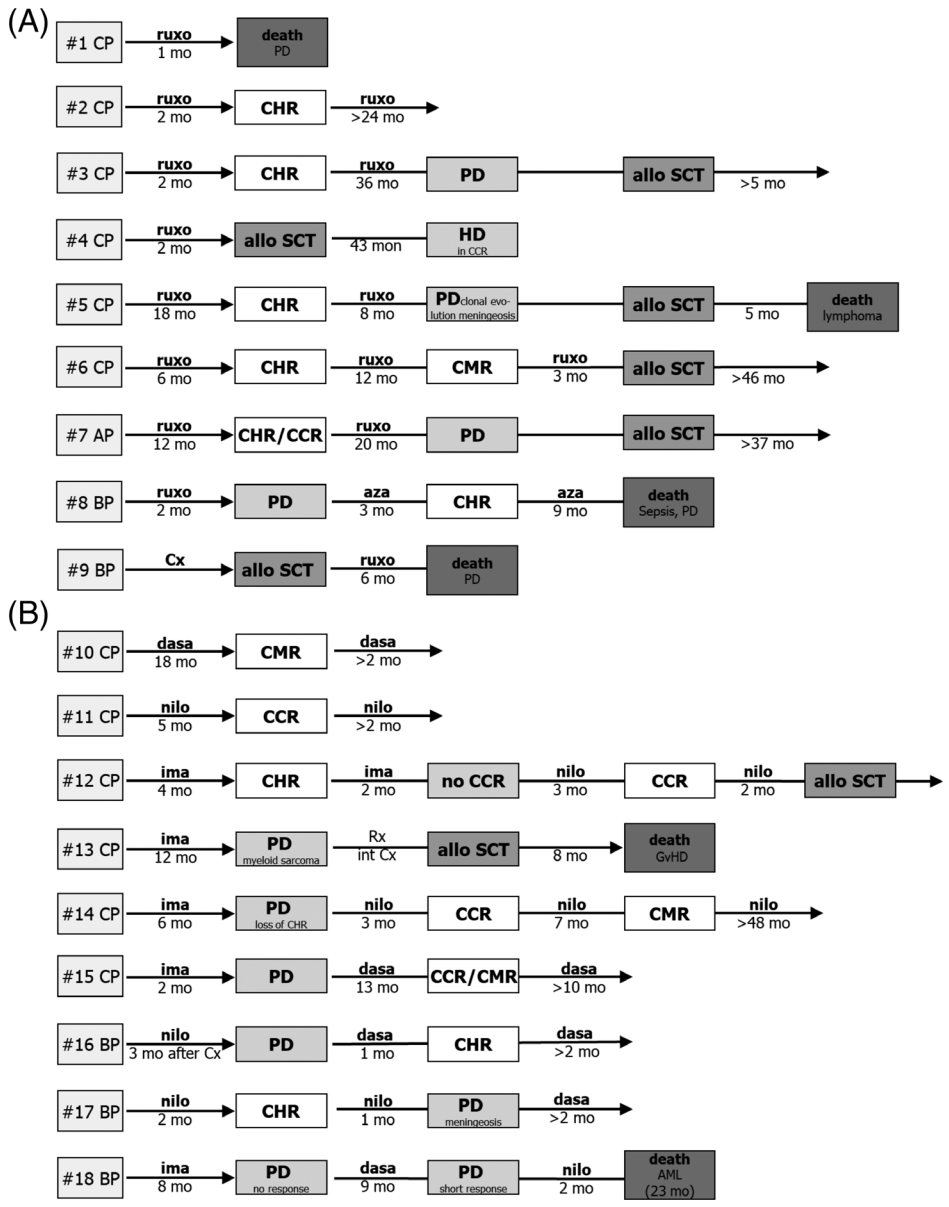

FIGURE 1 Treatment and follow-up. A) Nine patients with a *PCM1-JAK2* or *BCR-JAK2* fusion gene and B) Nine patients with an *ETV6-ABL1* fusion gene. Abbreviations: Allo SCT, allogenic stem cell transplantation; AP, accelerated phase; aza, azacytidine; BP, blast phase; CHR, complete hematological response; CCR, complete cytogenetic response; CMR, complete molecular response; CP, chronic phase; Cx, chemotherapy; HD, Hodgkin disease; mo, months; PD, progressive disease; ruxo, ruxolitinib

On imatinib, none of five patients achieved a CCR or CMR (Figure 1B). On nilotinib (patient no. 11) or dasatinib (patient no. 10), two patients in CP achieved CHR within 3 months and CCR, or CMR after 5 (patient 11) and 18 months (patient 10), respectively. After median 23 months (range, 3-60 months), five patients remain in CCR (n = 2, patients no. 11, 12) and/or CMR (n = 3; patients no. 10, 14, 15) on a second-generation TKI (nilotinib n = 2, patients 11, 14; dasatinib, n = 2, patients 10, 15) or after allo SCT (n = 1, patient no. 12), two patients (no. 13, 18) died.

3.6 | Inclusion of TKI treated *ETV6-ABL1* positive patients from the literature

The median age of the 23 adult patients with *ETV6-ABL1* positive MPN was 46 years (range 20-81 years) with a marked male predominance (17/23, 74%). When reported, leukocytosis (median 55 $\times$ 10^9/L, range 4-238 $\times$ 10^9/L) and eosinophilia (median 5.6 $\times$ 10^9/L, range 1.6-30.9 $\times$ 10^9/L) were present in 19/21 (90%) and 16/16 (100%) of patients, respectively. Initial histomorphological diagnoses in CP included MPN/MPN-eo (n = 7), aCML/CML-like disorder (n = 6) or MDS/MPN-U (n = 2). Four patients were diagnosed with primary BP, five patients developed secondary BP after median 14 months (range 6-36 months) . The phenotype was myeloid in five and lymphoid in four patients.[17,19,54]

Seventeen patients (74%) were initially treated with imatinib and nine patients were switched to a second-generation TKI due to relapsed or progressive disease. Six patients were primarily treated with nilotinib or dasatinib. A CHR was achieved on first line TKI in 13 patients (imatinib, n = 7; nilotinib, n = 4; dasatinib, n = 1), a CCR in seven patients (imatinib, n = 5; median 4 months, range 1-12 months) and a CMR in four patients (nilotinib, n = 1; dasatinib, n = 3). CCR was

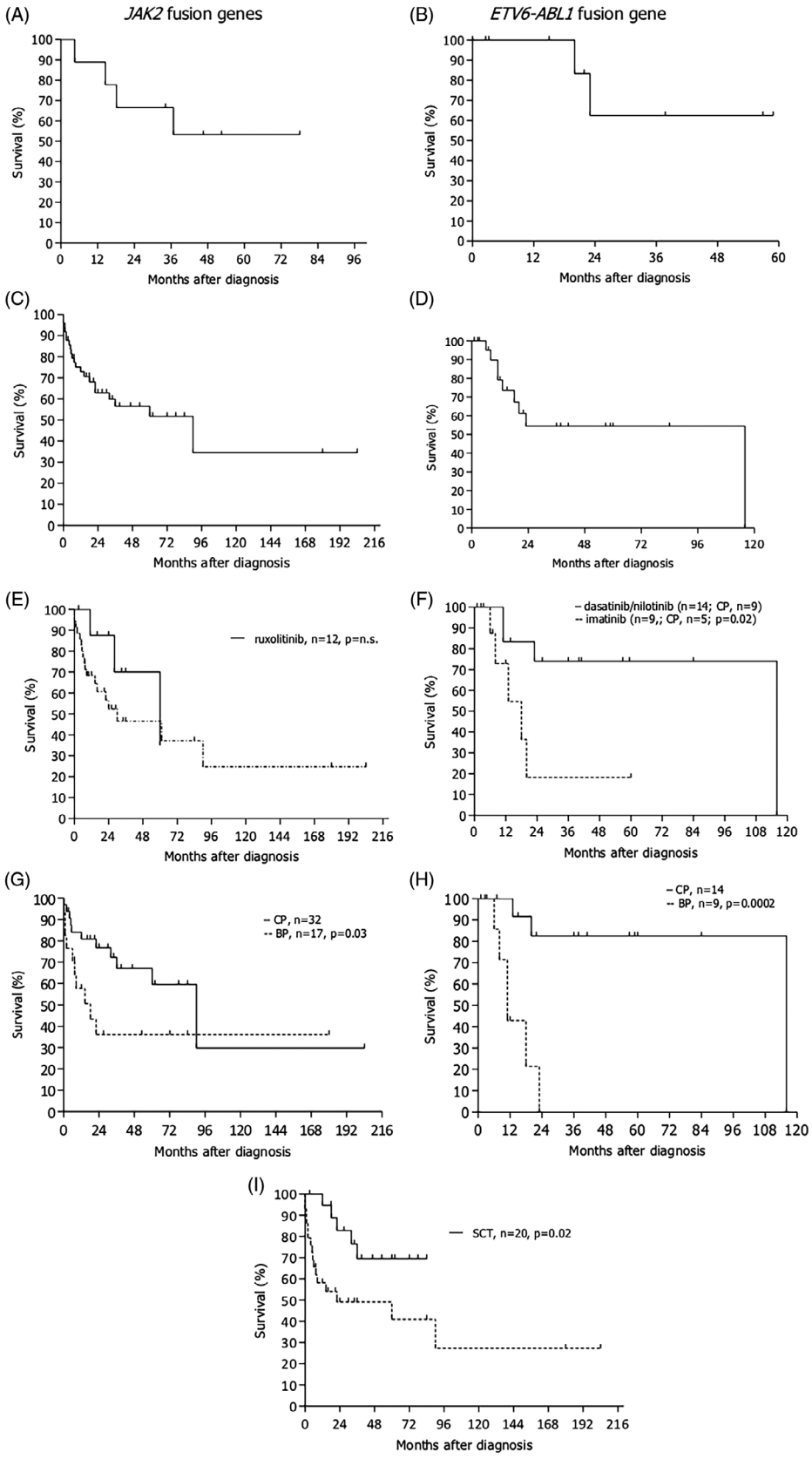

FIGURE 2 Overall survival according to fusion gene and treatment: A) Overall survival (OS) of nine patients with a *PCM1-JAK2* or *BCR-JAK2* fusion gene (median follow-up 36 months, range 4-78 months) and B) Nine patients with an *ETV6-ABL1* fusion gene (median follow-up 23 months, range 3-60 months). C) The OS of 49 patients with *JAK2* fusion gene (median 90 months, range 0-204 months). D) The OS of 23 patients with an *ETV6-ABL1* fusion gene treated with TKI (median follow-up 15 months, range 1-116 months). E), The OS of patients with a *JAK2* fusion gene treated with ruxolitinib (n = 12) compared to patients not treated with ruxolitinib censored for allo SCT (median OS 60 months, range 3-60 months vs 30 months, range 1-204 months; *P* = not significant). F) 17 patients (74%) with an *ETV6-ABL1* fusion gene were initially treated with imatinib, of which eight patients subsequently received a second-generation TKI due to progressive or relapsed disease. Six patients were initially treated with dasatinib or nilotinib. Patients treated with a second generation TKI had a better OS than patients only receiving imatinib (median 18 months, range 1-60 months, vs not reached, range 2-116 months; *P* = .02). G) OS of patients with a *JAK2* fusion gene in CP (n = 32) or BP (n = 17) (median 90.0 months, range 0-90 months, vs 18.2 months, range 0.1-48.0 months, *P* = .03). H, The OS of *ETV6-ABL1* positive patients in BP (n = 9) and CP (n = 14, median 11 months, range 2-23 months, vs not reached, range 1-116 months; *P* ≤ .001). Patients with a *JAK2* fusion gene after allo/auto SCT had a better OS than patients not receiving SCT (median not reached, range 0-204 months, vs 22 months, range 3-78 months; *P* = .02)

ongoing in two patients on imatinib after 4 and 60 months, respectively.[20,23] In nine patients, imatinib was switched to dasatinib (n = 5), nilotinib (n = 3) or ponatinib (n = 1) due to loss of CHR (n = 2), adverse effects (n = 2), loss of CCR (n = 2, T315I mutation) or resistance/progression (n = 3). Of these nine patients, eight patients achieved a CHR, five patients a CCR and six patients a CMR.

After a median follow-up of 18 months (range 1-116 months), nine of 24 patients died because of BP (n = 6) or disease-unrelated (n = 3; pneumonia after allo SCT at month 11+, n = 1; GvHD after allo SCT at month 8+, n = 1; pancreatic carcinoma at month 116, n = 1) and six of nine patients due to progressive disease including one patient with a T315I mutation. Patients in BP (n = 9) and patients exclusively treated with imatinib (n = 8) had a significant shorter OS than patients in CP (11 months, range 2-23 months, vs not reached, range 1-116 monrhs; P = .0002) or patients treated with a second generation TKI (18 months, range 1-60 months, vs 116 months, range 2-116 months; P = .02; Figure 2). Only three of 23 (13%) patients (no. 12, 13 and 24) underwent an allo SCT.

4 | DISCUSSION

We sought to evaluate disease characteristics and response to treatment with TKI in 18 patients with myeloid neoplasms and associated *JAK2* and *ETV6-ABL1* fusion genes. Moreover, we integrated our data into available cases from the literature to gain a more thorough insight into phenotype, treatment efficacy and prognosis of these distinct myeloid neoplasms.

In our series, the most notable clinical and morphological features of patients with *JAK2* fusion genes included a marked male predominance, lack of hypereosinophilia (≥1.5 × 10^9/L) in the majority of patients, pathognomonic giant paratrabecular islets of predominantly immature proerythroblasts,[36,37,57] and primary BP or relatively rapid progression to secondary BP in a significant proportion of patients. Patients can achieve CHR and CCR on ruxolitinib but it had to be stopped in all but one patient within the first 3 years, most frequently because of resistance, relapse or progression. In the extended analysis, three further patients were treated with ruxolitinib, with two patients achieving a CCR for more than 30 months.[12-15] There was, however, no long-term beneficial effect upon ruxolitinib (Figure 2). The aggressive phenotype (approximately 40% of patients in primary or secondary BP) and poor prognosis (median survival without transplant <24 months) of *JAK2* fusion gene positive myeloid neoplasms can possibly only be overcome by allo SCT and bridging with ruxolitinib should be considered. During follow-up, two patients developed a Burkitt-like B-cell lymphoma and an early stage Hodgkin lymphoma, respectively, which is noteworthy in the context of recent reports describing the development of high-grade B-cell lymphomas in ruxolitinib-treated patients.[58,59] Analysis of the Burkitt-like B-cell lymphoma revealed a complex karyotype including a t(8;9)(p22;p24), a rearrangement of *JAK2* by FISH analysis and a *PCM1-JAK2* fusion gene by RT-PCR, indicating lymphoid BP of the original disease. The patient with the Hodgkin lymphoma had received ruxolitinib only for 2 months and developed the lymphoma 43 months after early allogeneic SCT, while the *PCM1-JAK2* positive myeloid neoplasm was in complete remission. Lymphoma phenotype, short exposure to ruxolitinib and the late occurrence all call into question whether there is a causal relationship between ruxolitinib treatment and the lymphoma in this case.

The situation is different for *ETV6-ABL1* fusion gene associated myeloid neoplasms. Approximately 70 cases have been reported but despite a number of striking similarities with *FIP1L1-PDGFRA*, for example, marked male predominance, eosinophilia in almost all patients, frequent monocytosis, splenomegaly, marrow fibrosis, and presentation in either CP or primary/secondary BP, it has not been included in the WHO subgroup of MLN-eo. Imatinib is the obvious first-line treatment for *ETV6-ABL1* positive patients; however, we observed lack of response and/or early progression in most patients. After a median of 2 years, durable complete remissions were only observed on nilotinib, dasatinib or after allo SCT. We identified an additional 14 cases in the literature [16–27,53,54] with adequate data on response on TKI and follow-up. In concordance with our findings, imatinib can induce but not maintain long-term remissions.[25] Unfortunately, only limited data on TK-domain mutations are available which might explain the lack of response to and early progression on imatinib. However, second generation TKIs such as nilotinib and dasatinib are superior to imatinib with achievement of durable responses even after failure of imatinib. The overall rather poor prognosis of *ETV6-ABL1* positive eosinophilia-associated myeloid neoplasms is strongly associated with stage of disease (CP vs primary/secondary BP) and response to treatment with TKI.

We conclude that myeloid neoplasms with an associated *ETV6-ABL1* fusion gene are clear candidates for inclusion into the distinct subgroup of the WHO-classification "myeloid/lymphoid neoplasms with eosinophilia and rearrangement of a TK". Nilotinib and dasatinib are superior to imatinib and the best option for allo SCT may be the absence of a durable response or resistance to nilotinib or dasatinib. The *JAK2* fusions are associated with an aggressive phenotype and clinical course. Ruxolitinib can induce complete but frequently only transient remissions and early allo SCT should therefore be considered in all eligible patients.

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