

Current use of androgens in bone marrow failure disorders: a report from the Severe Aplastic Anemia Working Party of the European Society for Blood and Marrow Transplantation

Simona Pagliuca,¹ Austin G. Kulasekararaj,² Dirk-Jan Eikema,³ Brian Piepenbroek,⁴ Raheel Iftikhar,⁵ Tariq Mahmood Satti,⁵ Morag Griffin,⁶ Marica Laurino,⁷ Alphan Kupesiz,⁸ Yves Bertrand,⁹ Bruno Fattizzo,¹⁰ Ibrahim Yakoub-Agha,¹¹ Mahmoud Aljurf,¹² Paola Corti,¹³ Erika Massaccesi,¹⁴ Bruno Lioure,¹⁵ Marisa Calabuig,¹⁶ Matthias Klammer,¹⁷ Emel Unal,¹⁸ Depei Wu,¹⁹ Patrice Chevallier,²⁰ Edouard Forcade,²¹ John A. Snowden,²² Hakan Ozdogu,²³ Antonio Risitano²⁴ and Régis Peffault de Latour²⁵

¹Hôpitaux de Brabois, CHRU Nancy, and CNRS, Biopôle de l'Université de Lorraine, Vandoeuvre les Nancy, France; ²King's College Hospital-NHS Foundation Trust, NIHR/Wellcome King's Clinical Research Facility and King's College London, London, UK;

³EBMT Statistical Unit, Leiden, The Netherlands; ⁴EBMT Leiden Study Unit, Leiden, The Netherlands; ⁵Armed Forces Bone Marrow Transplant Centre, Rawalpindi, Pakistan; ⁶Saint James, Leeds Teaching Hospitals NHS Trust, Leeds, UK; ⁷Ospedale Policlinico San Martino, Genova, Italy; ⁸Akdeniz University Medical School Antalya, Turkey; ⁹Institut d'Hématologie et d'Oncologie Pédiatrique, Debrousse Hospital, Lyon, France; ¹⁰Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; ¹¹CHU de Lille, University of Lille, INSERM U1286, Lille, France; ¹²King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia;

¹³Clinica Pediatrica Università degli Studi Milano Bicocca, San Gerardo Hospital, Monza, Italy; ¹⁴IRCCS Istituto Giannina Gaslini, Genova, Italy; ¹⁵Institut de Cancérologie Strasbourg Europe (ICANS), Strasbourg, France; ¹⁶Hospital Clínico Universitario de Valencia, Valencia, Spain; ¹⁷St. George's Hospital, London, UK; ¹⁸University of Ankara, Ankara, Turkey; ¹⁹First Affiliated Hospital of Soochow University, Suzhou, China; ²⁰CHU Nantes, Nantes, France;

²¹CHU Bordeaux, F-33000, Bordeaux, France; ²²Sheffield Blood & Marrow Transplant and Cellular Therapy Program, Department of Hematology, Sheffield Teaching Hospitals NHS Trust, Sheffield, UK; ²³Baskent University Hospital, Adana, Turkey; ²⁴A.O.R.N. San Giuseppe Moscati, Avellino, Italy and ²⁵Hôpital Saint Louis, Assistance Publique-Hôpitaux de Paris, Paris, and French Reference Center for Aplastic Anemia, France

Correspondence: S. Pagliuca
s.pagliuca@chru-nancy.fr

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Supplementary Appendix

Current use of androgens in bone marrow failure disorders: a report from the Severe Aplastic Anemia Working Party of the European Society for Blood and Marrow Transplantation

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¹ Hôpitaux de Brabois, CHRU Nancy, and CNRS, Biopôle de l'Université de Lorraine, Vandoeuvre les Nancy, France

² King's College Hospital-NHS Foundation Trust, NIHR/Wellcome King's Clinical Research Facility, London, UK and King's College London, London

³ EBMT Statistical Unit, Leiden, Netherlands

⁴ EBMT Leiden Study Unit, Leiden, Netherlands

⁵ Armed Forces Bone Marrow Transplant Centre, Rawalpindi, Pakistan

⁶ Saint James, Leeds teaching Hospitals NHS trust, Leeds, United Kingdom.

⁷ Ospedale Policlinico San martino. Genova. Italy

⁸ Akdeniz University Medical School Antalya, Turkey

⁹ Institut d'Hématologie et d'Oncologie Pédiatrique, Debrousse Hospital, Lyon, France

¹⁰ Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

¹¹ CHU de Lille, University of Lille, INSERM U1286, Lille, France

¹² King Faisal Specialist Hospital & Research Centre Riyadh, Saudi Arabia

¹³ Clinica Pediatrica Università degli Studi Milano Bicocca, San Gerardo Hospital, Monza, Italy

¹⁴ IRCCS Istituto Giannina Gaslini, Genoa, Italy

¹⁵ Institut de cancérologie Strasbourg Europe (ICANS), Strasbourg, France

¹⁶ Hospital Clínico Universitario de Valencia Valencia Spain

¹⁷ St. George's Hospital, London, United Kingdom

¹⁸ University of Ankara, Ankara Turkey

¹⁹ First Affiliated Hospital of Soochow University, Suzhou, China

²⁰ CHU Nantes, Nantes, France

²¹ CHU Bordeaux, F-33000, Bordeaux, France

²² Sheffield Blood & Marrow Transplant and Cellular Therapy Program, Department of Hematology, Sheffield Teaching Hospitals NHS Trust, Sheffield, United Kingdom

²³ Baskent University Hospital, Adana, Turkey

²⁴ A.O.R.N. 'SAN.G MOSCATI' Avellino, Italy

²⁵ Hôpital Saint Louis, Assistance Publique-Hôpitaux de Paris, Paris, France and French Reference Center for Aplastic Anemia, France.

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Supplementary figures

Figure S1

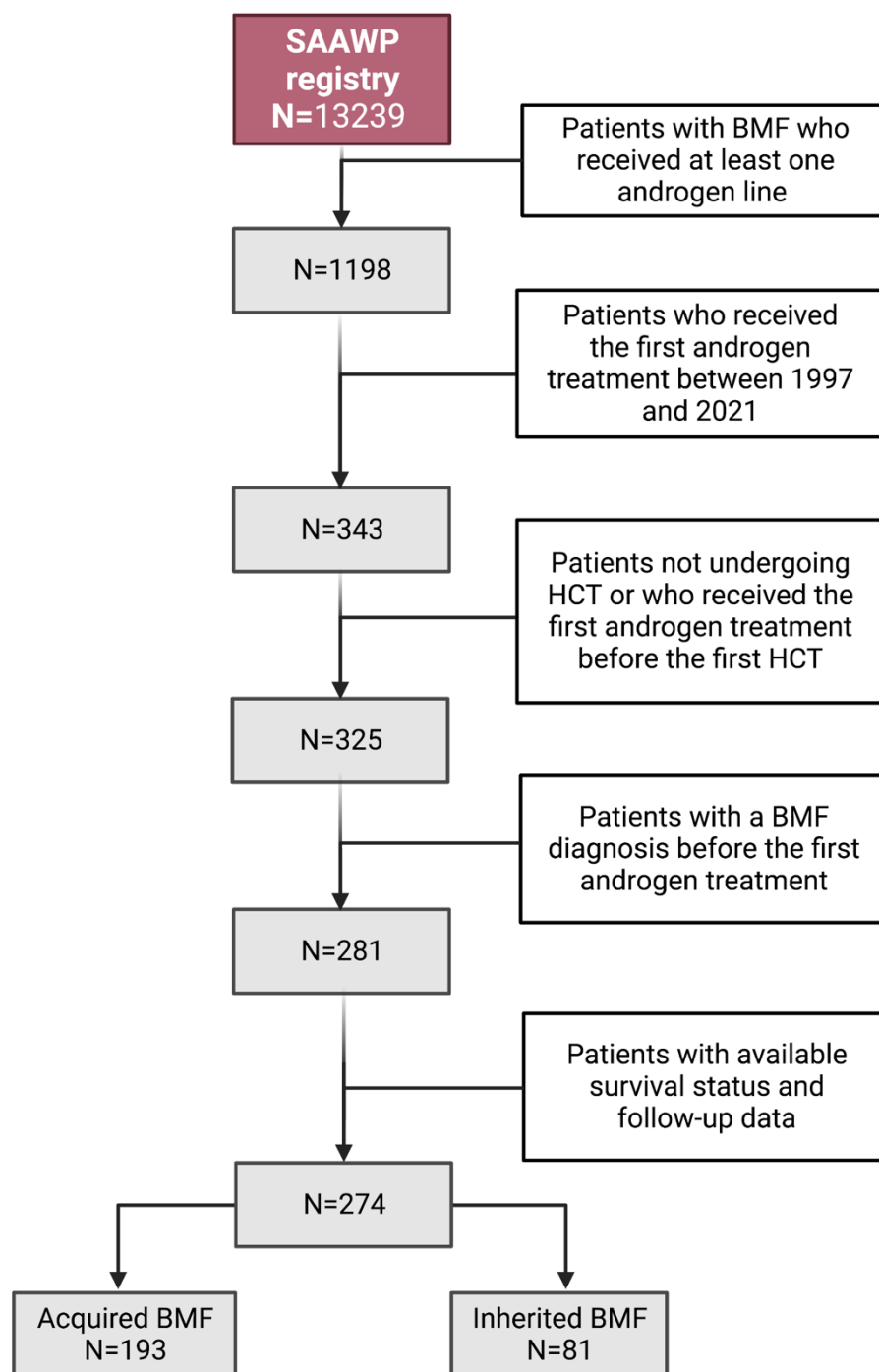


Figure S1: CONSORT diagram. Flow chart of selection criteria for the identification of androgen-treated patients in SAAWP registry. Abbreviations: BMF: Bone marrow failure; HCT: hematopoietic cell transplantation.

Figure S2

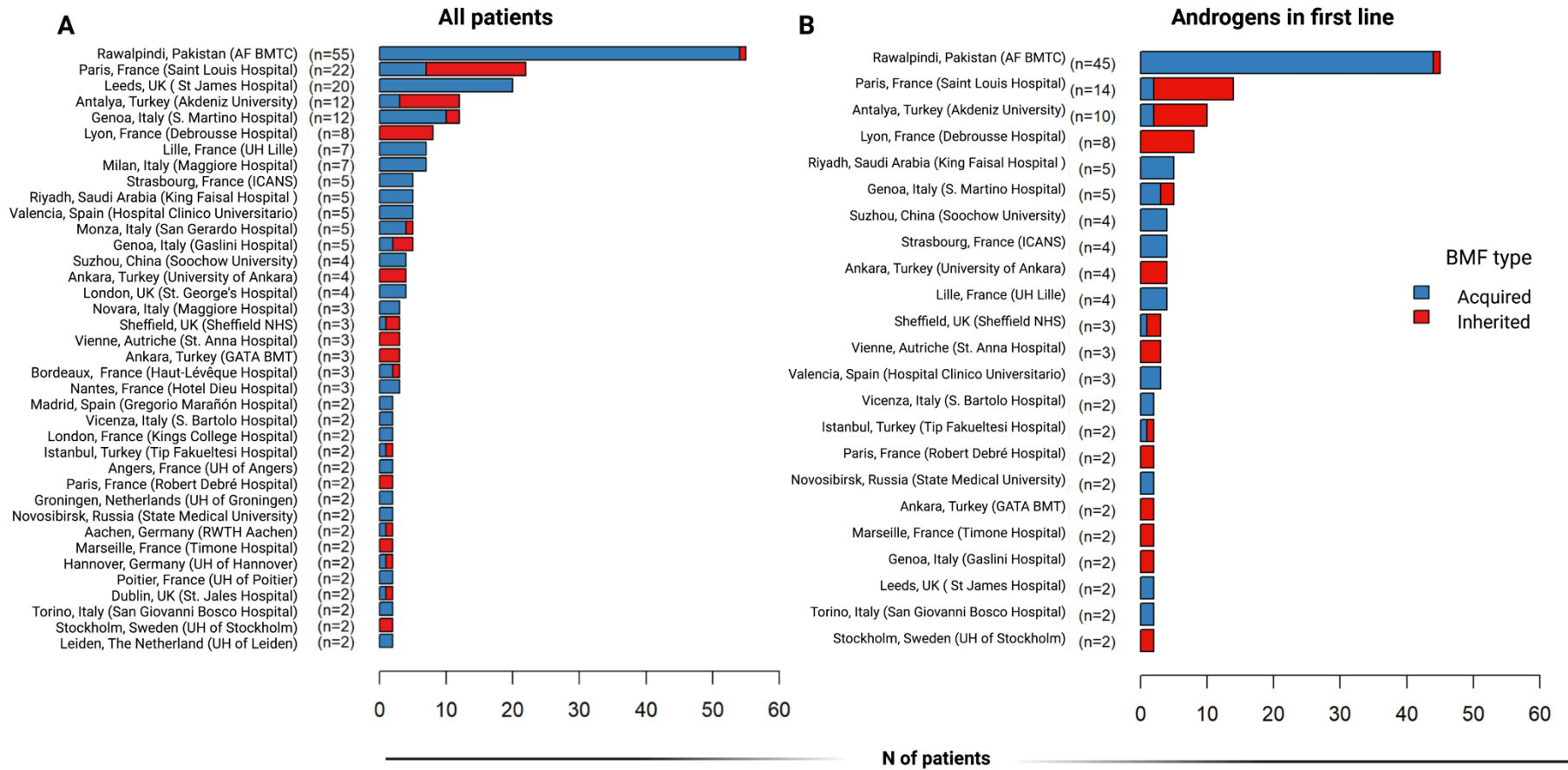


Figure S2: Center contribution. The bar graphs depict the number of patients by center, included in this study (only centers contributing with more than one patient are reported in this graph). **A:** all patients included in this study, **B:** only patients giving androgens in first line

Figure S3

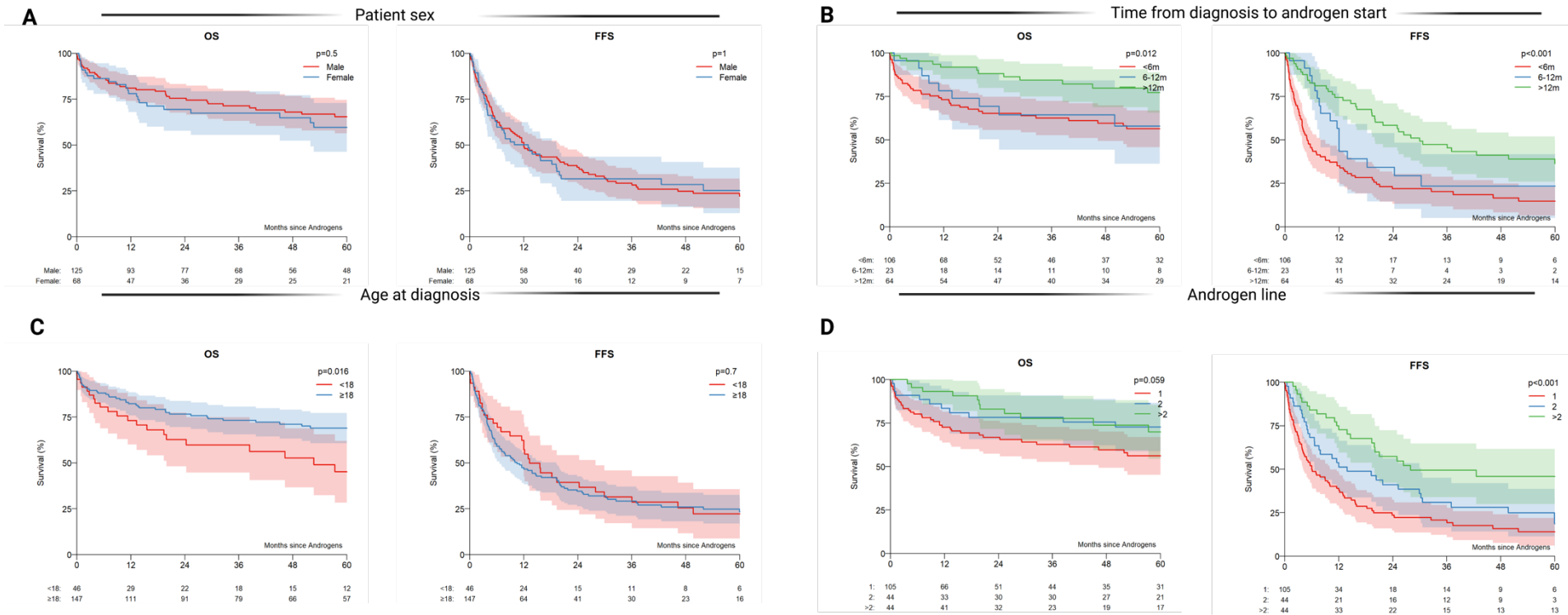


Figure S3: Univariable analysis of baseline variables impacting OS and FFS for acquired BMF. Kaplan-Meier estimations of overall survival (OS) and failure free survival (FFS) of patients with acquired BMF showing the impact of **A)** Patient sex, **B)** the time for androgen start, **C)** the age at diagnosis, **D)** the line of therapy (1: androgens given in first line, 2: androgen given as second line, >2: androgens given after the second line).

Figure S4

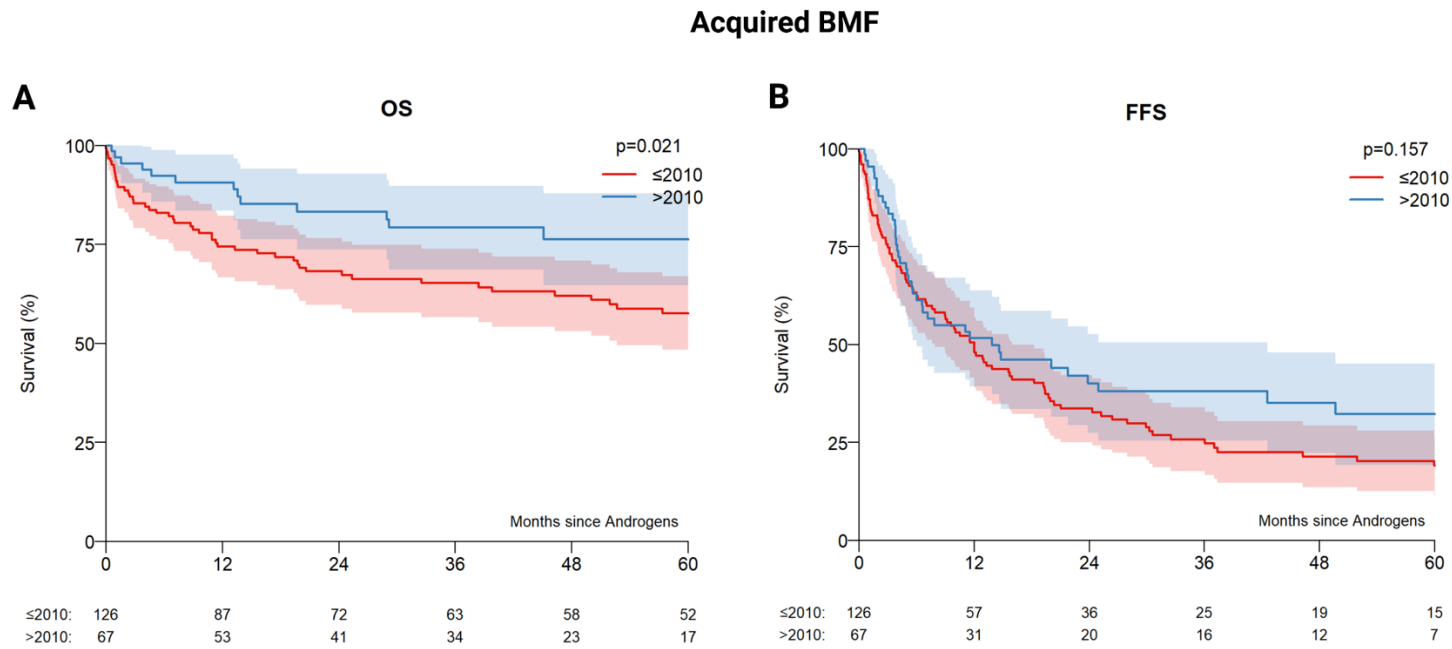


Figure S4: Univariable analysis of impact of year of treatment for acquired BMF. Kaplan-Meier estimations of overall survival (A) and failure free survival (B) of patients with acquired BMF according to the year of treatment.

Figure S5

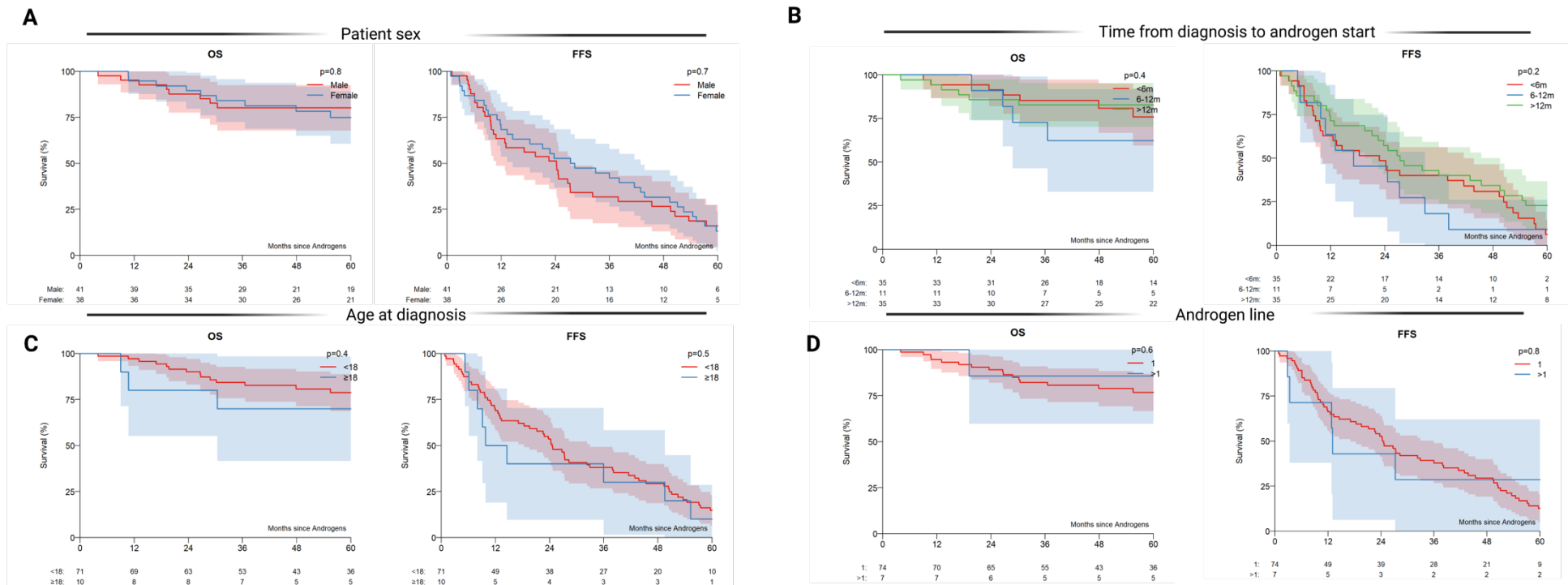


Figure S5: Univariable analysis of baseline variables impacting OS and FFS for inherited BMF. Kaplan-Meier estimations of overall survival (OS) and failure free survival (FFS) of patients with inherited BMF showing the impact of **A)** Patient sex, **B)** the time for androgen start, **C)** the age at diagnosis, **D)** the line of therapy (1: androgens given in first line, >1 androgen given after the first line).

Figure S6

Inherited BMF

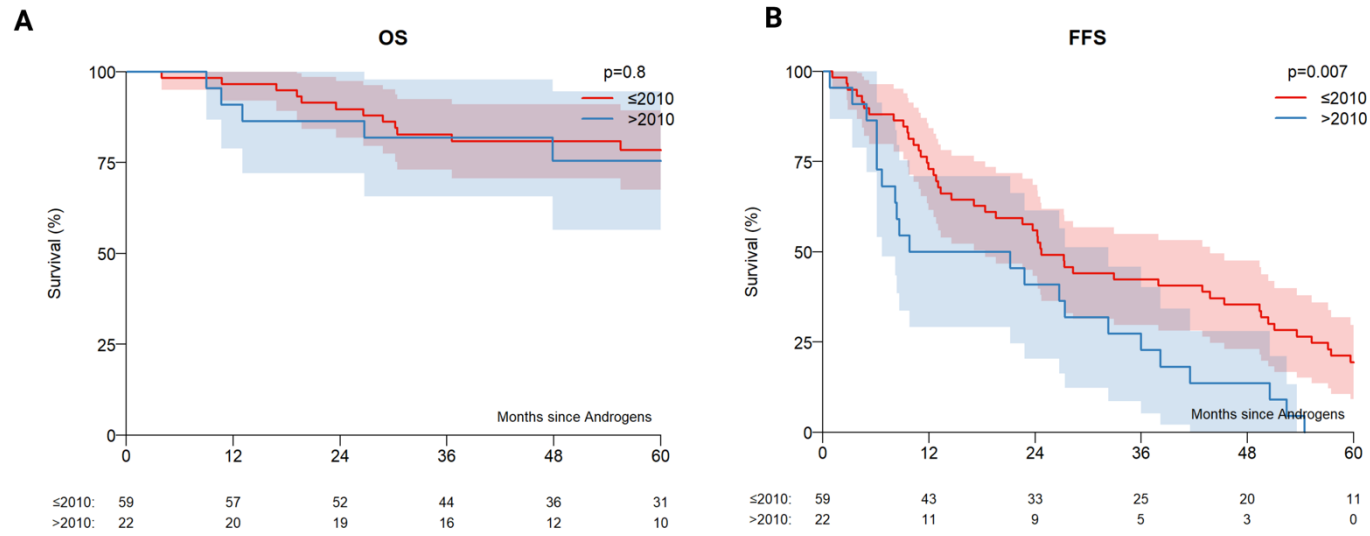


Figure S6: Univariable analysis of impact of year of treatment for inherited BMF. Kaplan-Meier estimations of overall survival and failure free survival of patients with inherited BMF according to the year of treatment.

Figure S7

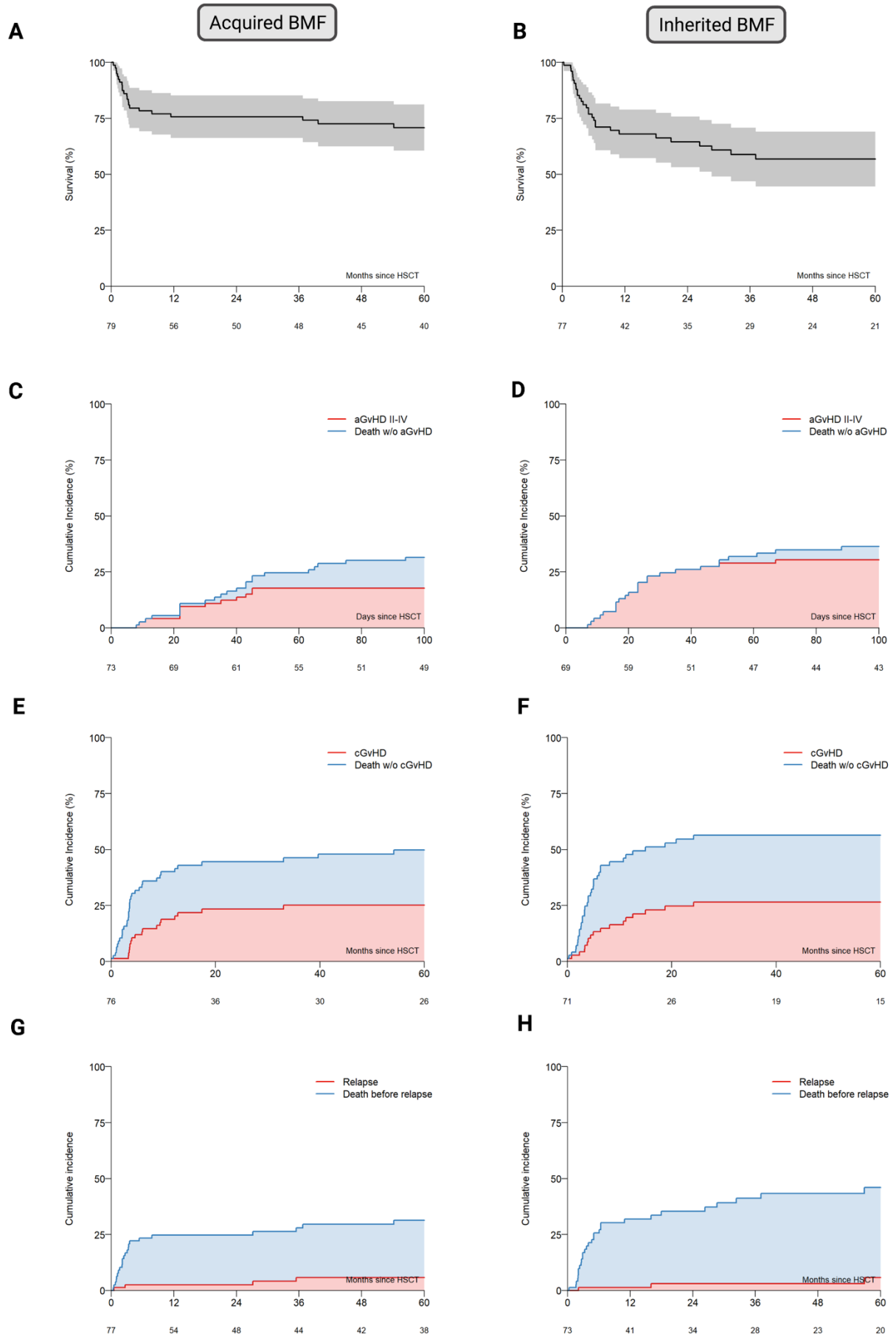


Figure S7: Outcome analysis in patients receiving an allogeneic hematopoietic cell transplantation after androgen treatment. A-B) Kaplan-Meyer estimates of OS in acquired and inherited BMF patients. C-D) Cumulative incidence of acute GvHD in acquired and inherited BMF patients (red); competing events are shown in blue. E-F) Cumulative incidence of chronic GvHD in acquired and inherited BMF patients (red); competing events are shown in blue. G-H) Cumulative incidence of relapse in acquired and inherited BMF patients (red); competing events are shown in blue.

Supplementary tables

Table S1

Table S1: Patient characteristics in acquired BMF group according to androgen-line					
	Variable	1st line		>1st line	
		N (%) / Median (IQR)	Missing	N (%) / Median (IQR)	Missing
All		105 (54.4%)		88 (45.6%)	
Type of diagnosis	Aplastic anemia	94 (89.5%)		82 (93.2%)	
	Pure red cell aplasia	4 (3.8%)		2 (2.3%)	
	Paroxysmal nocturnal hemoglobinuria (PNH)	5 (4.8%)		1 (1.1%)	
	Amegakaryocytic thrombocytopenia	1 (1.0%)		2 (2.3%)	
	Other acquired cytopenic syndromes	1 (1.0%)		1 (1.1%)	
Severity of Aplastic anemia	Moderate	15 (20.0%)	30 (28.6%)	24 (32.9%)	15 (17.0%)
	Severe	43 (57.3%)		31 (42.5%)	
	Very severe	17 (22.7%)		18 (24.7%)	
Sex	Male	73 (69.5%)		52 (59.1%)	
	Female	32 (30.5%)		36 (40.9%)	
Age at this diagnosis (years)		26.2 (16.8-43.2)		39.6 (18.9-57.9)	
Hemoglobin (g/dl) at diagnosis		7.8 (5.8-9.6)	31 (29.5%)	8 (6.3-9.4)	19 (21.6%)
Neutrophils (x10 ⁹ /L) at diagnosis		0.8 (0.4-1.2)	30 (28.6%)	0.7 (0.2-1.2)	21 (23.9%)
Platelets (x10 ⁹ /L) at diagnosis		8.5 (5-20)	29 (27.6%)	14 (8-25.2)	20 (22.7%)
Age at treatment initiation (years)		27 (17.3-43.2)		41.2 (22.1-60.1)	
Interval diagnosis-androgen treatment (months)		0.4 (0-2.1)		17.6 (8.2-28.5)	

Reticulocytes on first androgen treatment		30.5 (11.8-55.5)	97 (92.4%)	43 (20-60)	59 (67.0%)
Neutrophils on first androgen treatment		0.8 (0.4-1)	71 (67.6%)	1.2 (0.9-1.9)	40 (45.5%)
Platelets on first androgen treatment		7.5 (3.8-19.2)	69 (65.7%)	22 (15-39)	39 (44.3%)
Transfused on first androgen treatment (RBC)	No	9 (29%)	74 (70.5%)	3 (6%)	38 (43.2%)
	Yes	22 (71%)		47 (94%)	
Transfused on first androgen treatment (Platelets)	No	8 (28.6%)	77 (73.3%)	5 (10.2%)	39 (44.3%)
	Yes	20 (71.4%)		44 (89.8%)	
Number of RBC transfusions on first androgen treatment	<20 units	44 (71.0%)	43 (41.0%)	13 (33.3%)	49 (55.7%)
	20-50 units	8 (12.9%)		15 (38.5%)	
	>50 units	4 (6.5%)		6 (15.4%)	
	None	6 (9.7%)		5 (12.8%)	
Number of platelet transfusions on first androgen treatment	<20 units	42 (68.9%)	44 (41.9%)	17 (43.6%)	49 (55.7%)
	20-50 units	7 (11.5%)		11 (28.2%)	
	>50 units	4 (6.6%)		4 (10.3%)	
	None	8 (13.1%)		7 (17.9%)	
Number of lines before androgens	0	105 (100.0%)		0 (0.0%)	
	1	0 (0.0%)		44 (50.0%)	
	2	0 (0.0%)		25 (28.4%)	
	>2	0 (0.0%)		19 (21.6%)	
Type of Androgen	Danazol	3 (5.7%)	52 (49.5%)	25 (42.4%)	29 (33.0%)
	Nandrolone	0 (0.0%)		1 (1.7%)	
	Oxymetholone	45 (84.9%)		19 (32.2%)	
	Other	0 (0.0%)		2 (3.4%)	
	Nilevar	3 (5.7%)		2 (3.4%)	
	Danatrol	1 (1.9%)		5 (8.5%)	
	Testosterone	1 (1.9%)		5 (8.5%)	

Duration first androgen treatment (months)	Median (IQR)	4 (1.7-17.6)	53 (50.5%)	8.8 (3.4-25.2)	37 (42.0%)
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Abbreviations: BMF: bone marrow failure, IQR: interquartile range, RBC: red blood cell

Table S2

Table S2: Univariable stratified analysis											
Variable	Group	N	OS (95%CI lower-upper)				EFS (95%CI lower-upper)				
			12 months	36 months	60 months	p-value	12 months	36 months	60 months	p-value	
Acquired BMF	Sex	Male	125	81% (74-88%)	71% (63-80%)	65% (56-75%)	0.5	50% (41-59%)	29% (21-38%)	22% (14-30%)	>0.99
		Female	68	78% (68-88%)	67% (56-79%)	60% (46-73%)		50% (38-62%)	32% (20-44%)	25% (13-38%)	
	Age	<18	46	73% (60-86%)	60% (45-75%)	45% (28-62%)	0.016	60% (45-74%)	31% (17-46%)	22% (9-36%)	0.7
		18	147	82% (76-89%)	73% (66-81%)	69% (61-77%)		47% (38-55%)	29% (21-37%)	23% (15-31%)	
	Months from diagnosis to androgen start	<12m	129	74% (66-82%)	63% (54-72%)	56% (47-66%)	0.003	37% (29-46%)	21% (13-28%)	16% (9-24%)	<0.001
		>12m	64	92% (85-99%)	84% (75-94%)	77% (66-89%)		74% (64-85%)	47% (34-60%)	36% (23-50%)	
	Androgen line	1	105	73% (64-81%)	63% (53-73%)	56% (45-67%)	0.06	38% (28-48%)	21% (12-29%)	14% (6-22%)	<0.001
		2	44	83% (72-95%)	78% (66-91%)	73% (59-87%)		51% (36-66%)	31% (17-45%)	19% (4-33%)	
		>2	44	93% (86-100%)	78% (65-91%)	70% (54-85%)		75% (62-88%)	49% (34-65%)	46% (30-62%)	
	Year of androgen treatment	2010	126	74% (67-82%)	65% (57-74%)	58% (48-67%)	0.021	49% (40-58%)	26% (18-34%)	19% (11-27%)	0.16
>2010		67	91% (84-98%)	79% (69-90%)	76% (65-88%)	52% (39-64%)		38% (26-51%)	32% (19-45%)		
Inherited BMF	Sex	Male	41	95% (89-100%)	80% (68-92%)	80% (68-92%)	0.8	63% (49-78%)	32% (17-46%)	16% (4-27%)	0.7
		Female	38	95% (88-100%)	84% (72-96%)	75% (61-89%)		68% (54-83%)	42% (26-58%)	13% (2-24%)	
	Age	<18	71	97% (93-100%)	84% (76-93%)	79% (69-89%)	0.4	69% (58-80%)	38% (27-49%)	15% (6-23%)	0.5
		18	10	80% (55-100%)	70% (42-98%)	70% (42-98%)		50% (19-81%)	30% (2-58%)	10% (0-29%)	
	Months from diagnosis to androgen start	<12m	46	96% (90-100%)	82% (71-93%)	73% (58-87%)	0.5	63% (49-77%)	35% (21-49%)	7% (0-15%)	0.11
		>12m	35	94% (87-100%)	83% (70-95%)	83% (70-95%)		71% (56-86%)	40% (24-56%)	23% (9-37%)	
	Androgen line	1	74	95% (89-100%)	82% (73-91%)	77% (67-87%)	0.6	66% (55-77%)	38% (27-49%)	13% (5-20%)	0.8
		>1	7	100% (0-100%)	86% (60-100%)	86% (60-100%)		71% (38-100%)	29% (0-62%)	29% (0-62%)	
	Year of androgen treatment	2010	59	97% (92-100%)	83% (73-92%)	78% (67-89%)	0.8	73% (62-84%)	42% (30-55%)	19% (9-30%)	0.007
		>2010	22	91% (79-100%)	82% (66-98%)	76% (57-95%)		50% (29-71%)	23% (5-40%)		

Abbreviations: BMF: bone marrow failure, IQR: interquartile range, N: number; CI: confident interval, OS: Overall survival, FFS: Failure free survival.

Table S3

Table S3: Cumulative incidence of toxicity							
	Type of toxicity	N	N events	Median time to toxicity (months) (IQR)	Cumulative incidence of toxicity (95% CI)		
					12 months	36 months	60 months
Acquired BMF	Liver toxicity	110	13	2.8 (0.5 - 5.7)	11% (5-18%)	13% (6-19%)	13% (6-19%)
	Gastrointestinal toxicity	109	4	6.3 (4.5 - 7.3)	4% (0-8%)	4% (0-8%)	4% (0-8%)
	Psychiatric toxicity	111	1	18.1 (18.1 - 18.1)	0% (0-0%)	1% (0-3%)	1% (0-3%)
	Renal toxicity	109	3	5.4 (4.4 - 5.8)	3% (0-6%)	3% (0-6%)	3% (0-6%)
	Endocrinological toxicity	0					
Inherited BMF	Liver toxicity	31	4	22.8 (8 - 41.5)	6% (0-15%)	10% (0-20%)	13% (1-25%)
	Gastrointestinal toxicity		0				
	Psychiatric toxicity		0				
	Renal toxicity		0				
	Endocrinological toxicity	31	2	15.1 (11.5 - 18.7)	3% (0-9%)	6% (0-15%)	6% (0-15%)

Abbreviations: BMF: bone marrow failure, IQR: interquartile range, N: number; CI: confident interval

Table S4

Table S4: Patient characteristics of the transplanted cohort					
	Group	Acquired		Inherited	
		N (%) / median (IQR)	Missing	N (%) / median (IQR)	Missing
		N=82		N=70	
Age at this treatment	Median (IQR)	30.1 (22-42.5)		11.6 (7.9-15.5)	
Interval diagnosis-tx in months	Median (IQR)	19.7 (9.6-55.6)		41 (16.7-70.3)	
Stem cell source	BM	45 (58%)	4 (4.9%)	37 (48.1%)	2 (4.5%)
	PB	24 (31%)		25 (32.5%)	
	CB	4 (5%)		1 (1.3%)	
	Mixed graft	5 (6%)		14 (18.20%)	
Type of donor	Identical sibling	24 (30.4%)	3 (3.7%)	21 (27.30%)	1 (2.3%)
	Matched other relative			5 (6.50%)	
	Matched unrelated	11 (13.9%)		11 (14.30%)	
	Mismatched relative	10 (12.7%)		9 (11.70%)	
	Mismatched unrelated	10 (12.7%)		12 (15.60%)	
	Unrelated	24 (30.4%)		19 (24.70%)	
Interval start first androgen treatment to first tx (months)	Median (IQR)	14.3 (4.9-32.4)		25.1 (9.9-50.5)	
GvHD Prophylaxis	CNI/MTX	47 (62%)	6 (7%)	12 (17%)	8 (10%)
	CNI alone	13 (17%)		33 (47%)	
	CNI/MMF	11 (14%)		23 (33%)	
	Other	5 (7%)		2 (3%)	
Conditioning regimen	RIC	43 (56.6%)	6 (7.3%)	55 (76.4%)	6 (7.7%)
	MAC	33 (43.4%)		17 (23.6%)	

Abbreviations: BMF: bone marrow failure; IQR: interquartile range, N: number; tx: transplant; GvHD: graft versus host disease; CNI: calcineurin inhibitor; MTX: methotrexate ; MMF : Mycophenolate mofetil ; RIC : reduced intensity conditioning ; MAC : myeloablative conditioning regimen ; NM : non myeloablative