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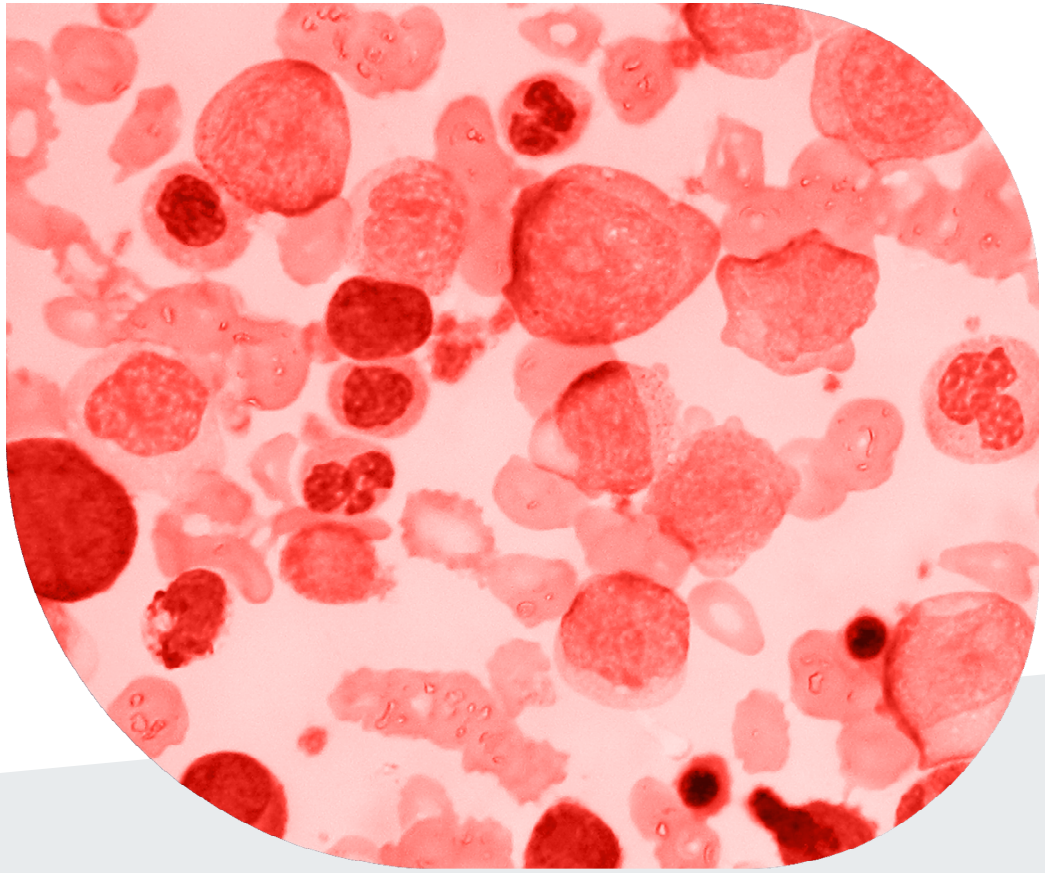
CML: The use of allogeneic stem cell transplantation



May 2022

Edited by Prof. Gianantonio Rosti

Learning objectives

Following review of these slides the reader should understand:

- How ASCT fits into the treatment landscape for the management of CML
- The purpose of ASCT and appropriate patient selection
- An overview of key safety and efficacy outcomes in patients with CML undergoing ASCT
- An overall summary of the clinical implications and strategies of ASCT in CML

ASCT, allogeneic stem cell transplantation; CML, chronic myeloid leukemia.

How ASCT fits into the current treatment landscape for CML

- Long-term follow-up analyses indicate that by 5 years an estimated 40% of patients with CML require a change of therapy due to resistance, intolerance, or other indications. Developing resistance to TKIs and requiring multiple changes of therapies has been shown to decrease survival probability[1]
- ASCT was developed to replace the blood-forming cells that are destroyed during high-dose chemotherapy.[2] Originally considered as frontline treatment in the early 90s, ASCT shifted to third- or fourth-line due to the introduction of TKIs in the 2000s[3]
- Candidates for ASCT in 2022 need to meet certain criteria: patients in CP with resistance or intolerance to multiple TKIs or patients with advanced disease after conventional therapy such as TKIs with or without chemotherapy. Patients should ideally have a low EBMT score[4–7]

CML therapy primary goals[8]

ASCT, allogeneic stem cell transplantation; CML, chronic myeloid leukemia; CP, chronic phase; DMR, deep molecular response; EBMT, European Society for Bone and Marrow Transplantation; OS, overall survival; TFR, treatment-free remission; TKI, tyrosine kinase inhibitors.

1. DeAngelo D, et al. *OncLive 2022*. [Accessed 10 April 2022]; 2. Yassine et al. *Hematology/Oncology and Stem Cell Therapy* 2021; 3. Axdorph U, et al. *British Journal of Haematology* 2002;118:1048–54; 4. Atallah E and Sweet K. *Current Hematologic Malignancy Reports* 2020;16:433–39; 5. Nair A, et al. *Biology of Blood and Marrow Transplantation* 2015; 21:1437–44; 6. Gratwohl A. *Bone Marrow Transplantation* 2011;47:749–56; 7. Innes AJ, et al. *Nat Rev Clin Oncol* 2016;13:79–91; 8. Baccarani M, et al. *Leukemia* 2022;36:1227–36.

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TKI response according to guidelines

- Failure to respond to TKIs is defined by specific guidelines (ELN, NCCN, and ESMO)[1–4]

	TKI therapy failure		
Time	**ELN (2020)[2]**	**NCCN (2021)[3]**	**ESMO (2017)[4]**
3 months	*BCR-ABL1* >10% in PCR test if confirmed within 1–3 months	*BCR-ABL1* >10%	No CHR Ph >95%
6 months	*BCR-ABL1* >10% in PCR test	*BCR-ABL1* >10%	Ph >35% *BCR-ABL* >10%
12 months	*BCR-ABL1* >1% in PCR test	*BCR-ABL1* >1%	Ph >1% *BCR-ABL* >1%
Then and at any time during treatment	*BCR-ABL1* >1% in PCR test High-risk ACAs in cells with the Philadelphia chromosome	-	Relapse, loss of MMR (*BCR-ABL1* >0.1%)

ACA, additional chromosomal aberration; CHR, complete hematologic response; ELN, EuropeanLeukemia net; ESMO, European Society for Medical Oncology; MMR, major molecular remission; NCCN, National Comprehensive Cancer Network; PCR, polymerase chain reaction; Ph, Philadelphia; TKI, tyrosine kinase inhibitor.

1. Hochhaus A, et al. *Leukemia* 2020;34:966–84; 2. ELN. *Recommendations for Treating People Living with CML* 2020. [Accessed 28 April 2022]; 3. NCCN. *NCCN Guidelines for Patients Chronic Myeloid Leukemia* 2021. [Accessed 28 April 2022]; 4. Hochhaus A, et al. *ESMO Interactive Guidelines* 2017. [Accessed 28 April 2022].

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Recommendations for ASCT by disease phase

Disease phase	Disease characteristics warranting the need to consider ASCT
Chronic phase	Poor response to >2 TKIs[1]
Advanced phase[1]	Patients with appearance of high-risk ACAs as a sign of progression, presence of *T315I* mutation[1,2]
	Resistance to a second-generation TKI in first-line or second-line[2]
	Failure with ponatinib[1,2]
	Accelerated phase at diagnosis[1]
	Evolution into accelerated phase whilst on TKI[1,3]
Blast phase	ASCT as soon as possible: patients returning to a second CP (CP2) before ASCT have improved transplantation outcomes [1,3]

ACA, additional chromosomal aberrations; ASCT, allogeneic stem cell transplantation; CP, chronic phase; TKI; tyrosine kinase inhibitor.

1. ELN. *Recommendations for Treating People Living with CML* 2020. [Accessed 28 April 2022]; 2. Hochhaus A, et al. *ESMO Interactive Guidelines* 2017. [Accessed 28 April 2022];
3. Pavlů J and Apperley J. *Current Hematologic Malignancy Reports* 2012;8:43–51.

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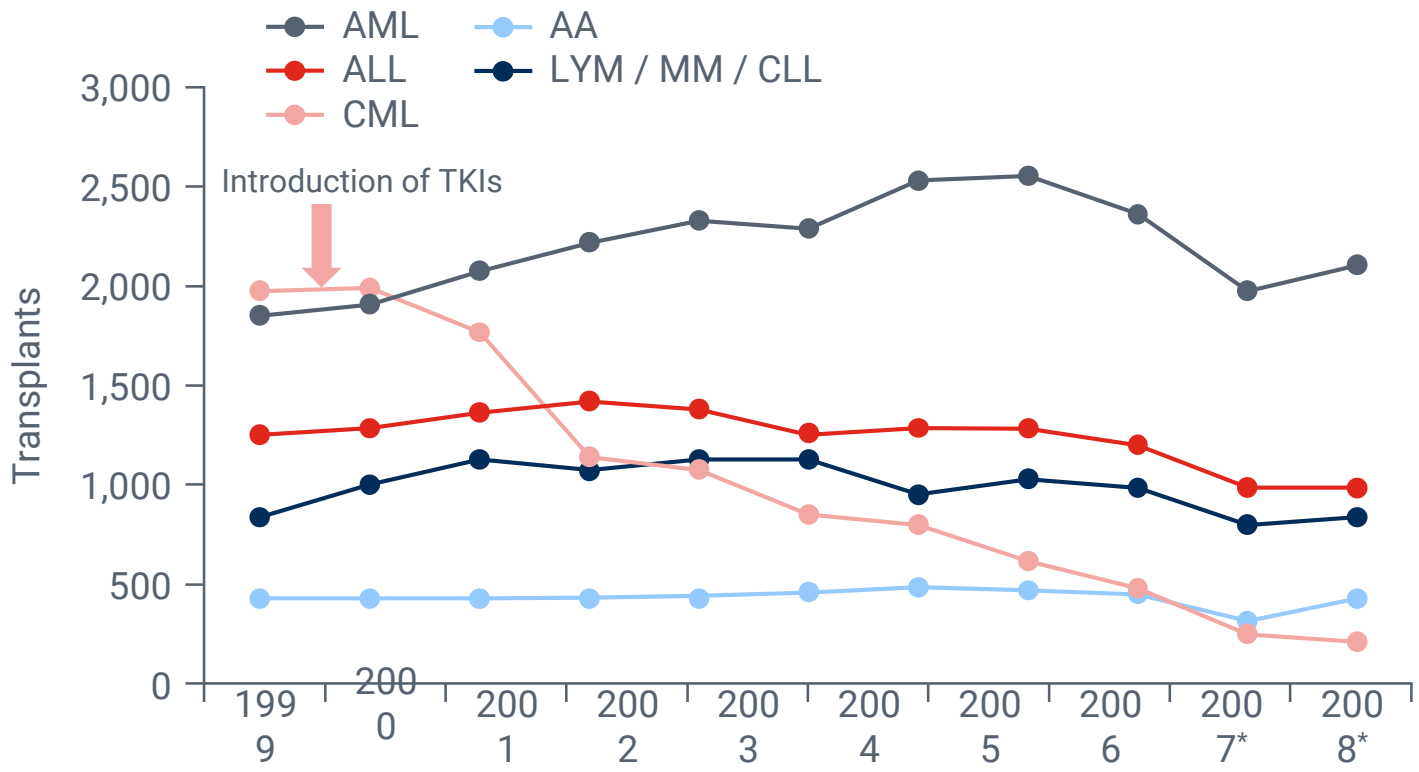
Advances in ASCT

- Advances within ASCT are evident and include an increase in the number of registered volunteer donors, the creation of large cord blood banks, and advances in immunosuppression and supportive care.[1]
- However, since the advent of TKIs, the number of ASCTs registered with CIBMTR has decreased.[2] In 2020, less than 200 of over 10,000 allotransplants reported to the CIBMTR were for CML[3]

Number of allogeneic transplants, by disease, registered with CIBMTR 1998-2008



*Data incomplete.
ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; AA, aplastic anemia; ASCT, allogeneic stem cell transplantation; CIBMTR, Center for International Blood and Marrow Transplant Research; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; LYM, lymphoma; MM, multiple myeloma; TKI, tyrosine kinase inhibitor.
1.Veldman R, et al. *Discovery Medicine* 2003;16:179–86; 2. Auletta J, et al. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR US summary slides, 2021; 3. Baccarani M, et al. *Leukemia* 2022;36:1227–36.

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Considerations for ASCT by EBMT score

Risk factor	Score points
Age of patient (years)	
<20	0
20-40	1
>40	2
Disease stage	
Early	0
Intermediate	1
Late	2
Time interval from diagnosis to transplant (months)	
<12	0
>12	1

Risk factor	Score points
Donor type	
HLA-identical sibling donor	0
Unrelated donor, other	1
Donor recipient sex combination	
All other	0
Female donor, male recipient	1

ASCT, allogeneic stem cell transplantation; EBMT, European Group for Marrow and Blood Transplantation; HLA, human leukocyte antigen

1. Gratwohl A, et al. The EBMT risk score. *Bone Marrow Transplantation* 2011;47:749–56.

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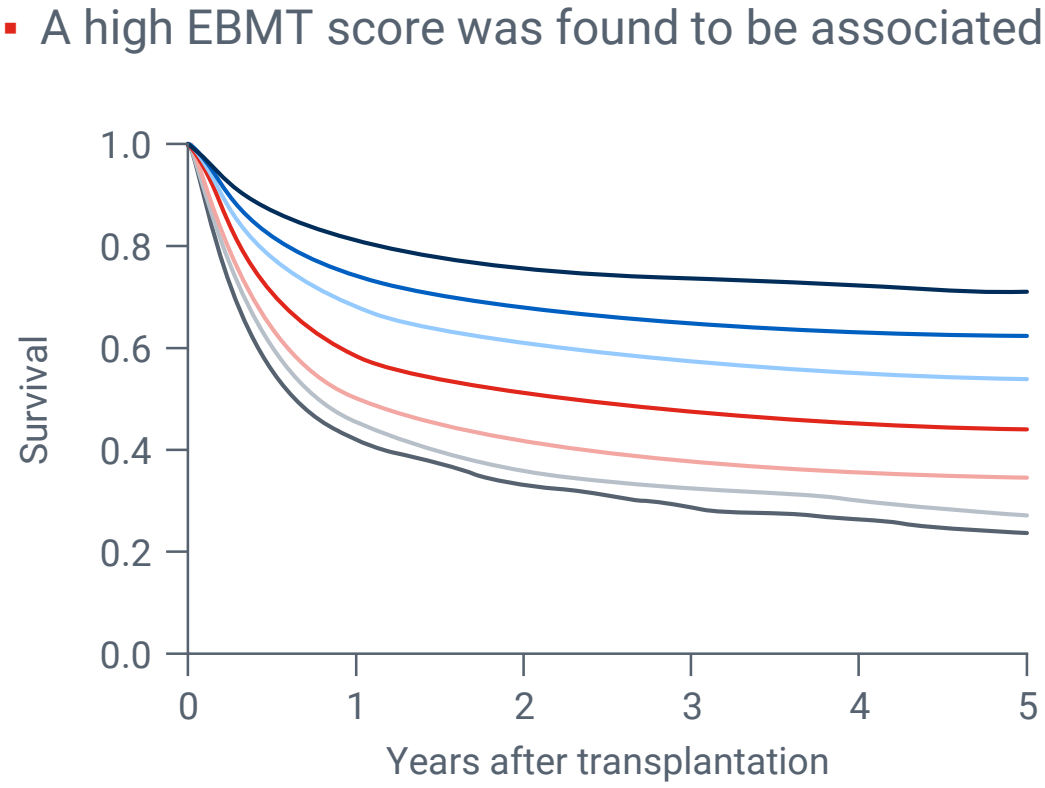
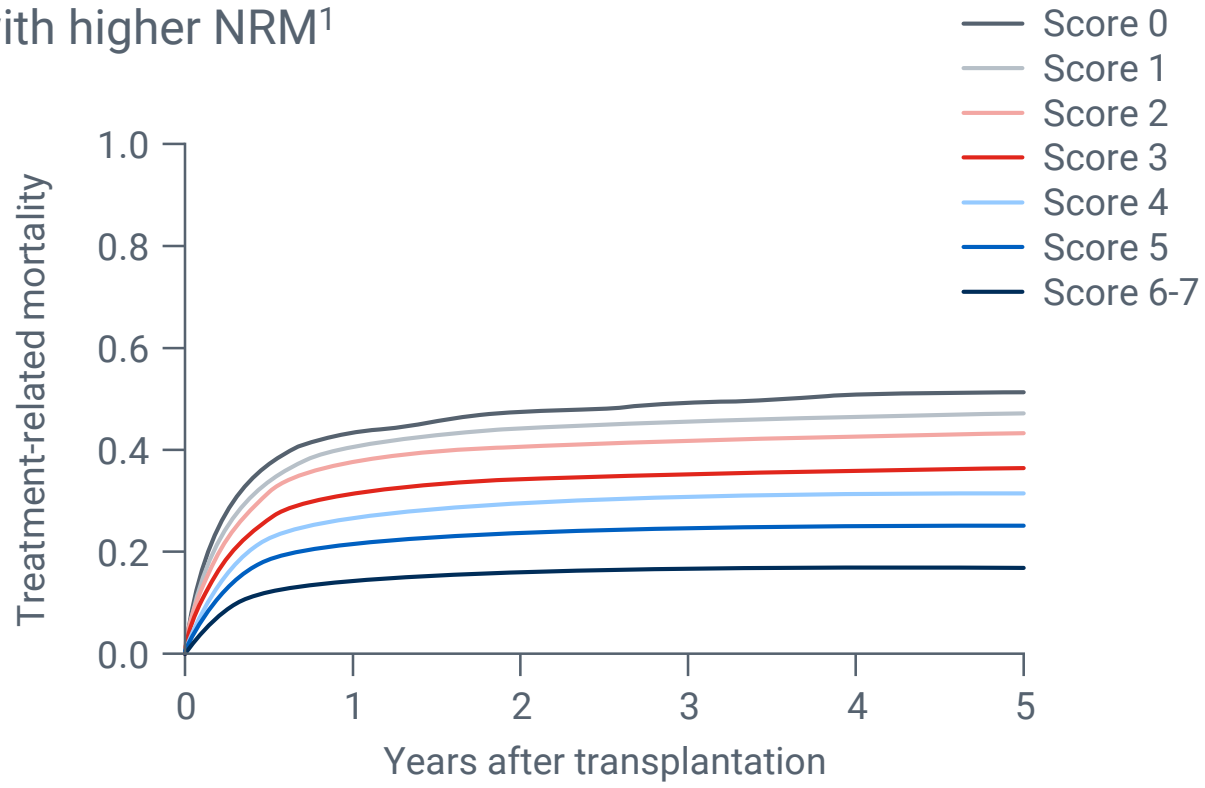
Considerations for ASCT by EBMT score

- The EBMT Risk Score calculates the chances and risks of ASCT for a patient pre-transplant by assessing five factors and generating a score from 0 as best and 7 as worst in an additive way[1]
- A high EBMT score was found to be associated with higher NRM[1]





ASCT, allogeneic stem cell transplantation; EBMT, European group for blood and bone marrow transplantation; NRM, non-relapse mortality; OS, overall survival.

1. Gratwohl A, et al. The EBMT risk score. *Bone Marrow Transplantation*. 2011;47:749–56.

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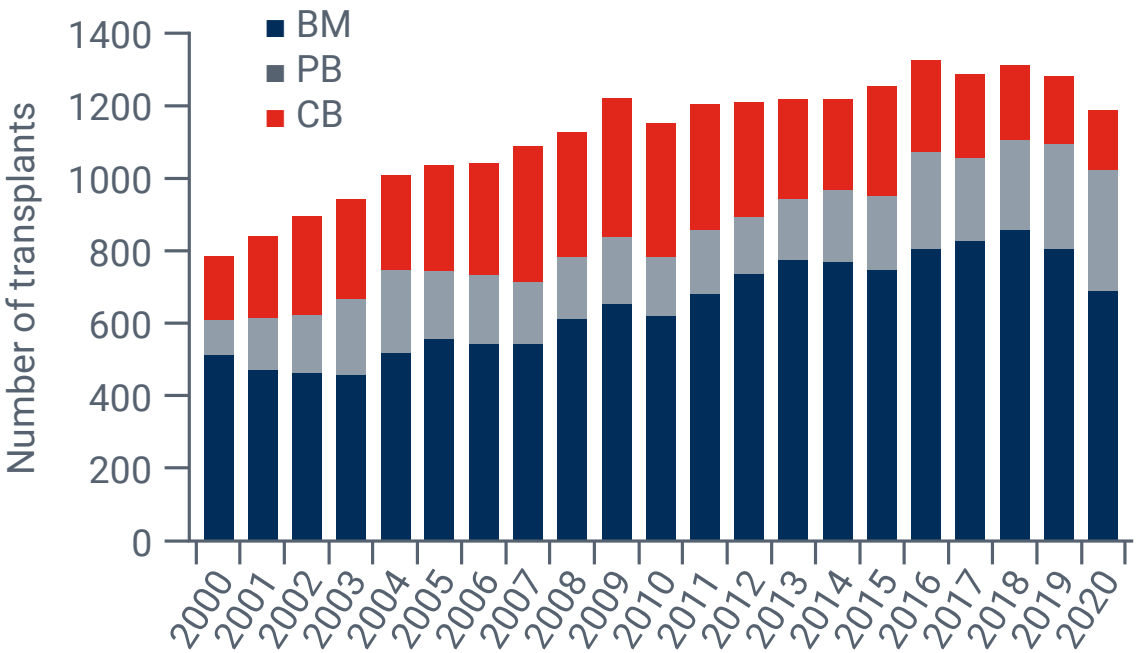
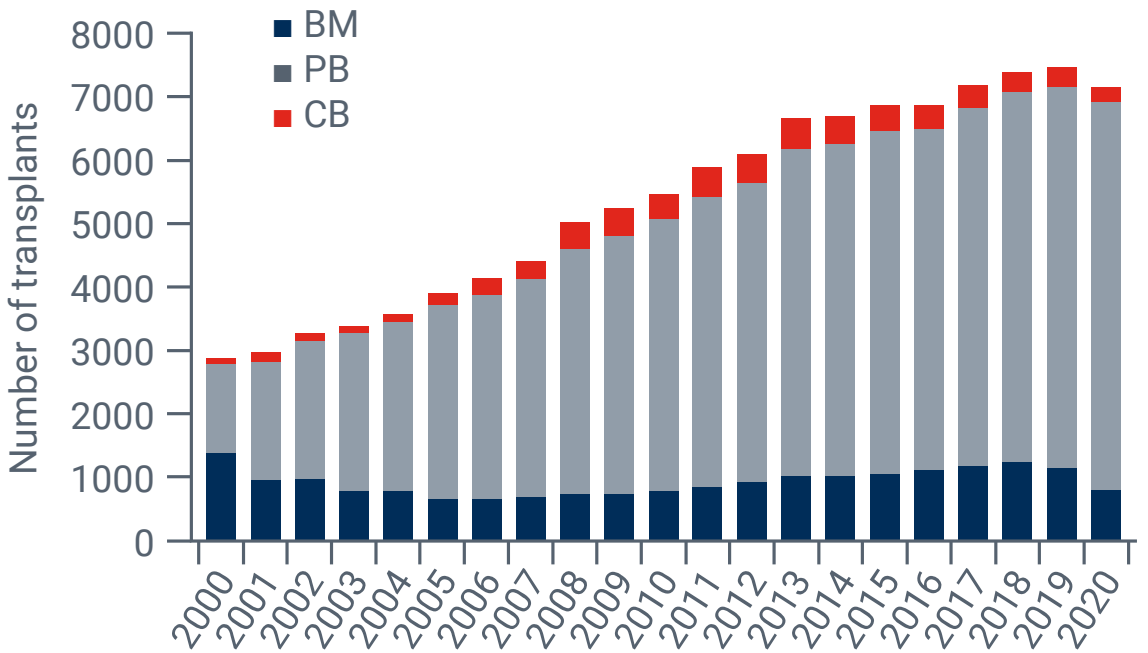
Stem cell sources in ASCT

- ASCT uses stem cells from a donor, either bone marrow, peripheral blood or cord blood, with these graft sources varying according to the demographics of the recipient[1]

Number of allogeneic HCTs in the US in recipients aged <18 years by graft source



Number of allogeneic HCTs in the US in recipients aged ≥18 years by graft source



ASCT, allogeneic stem cell transplantation; BM, bone marrow; CB, cord blood; HCT, hematopoietic cell transplant; PB, peripheral blood.

1. Auletta J, et al. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR US summary slides, 2021.

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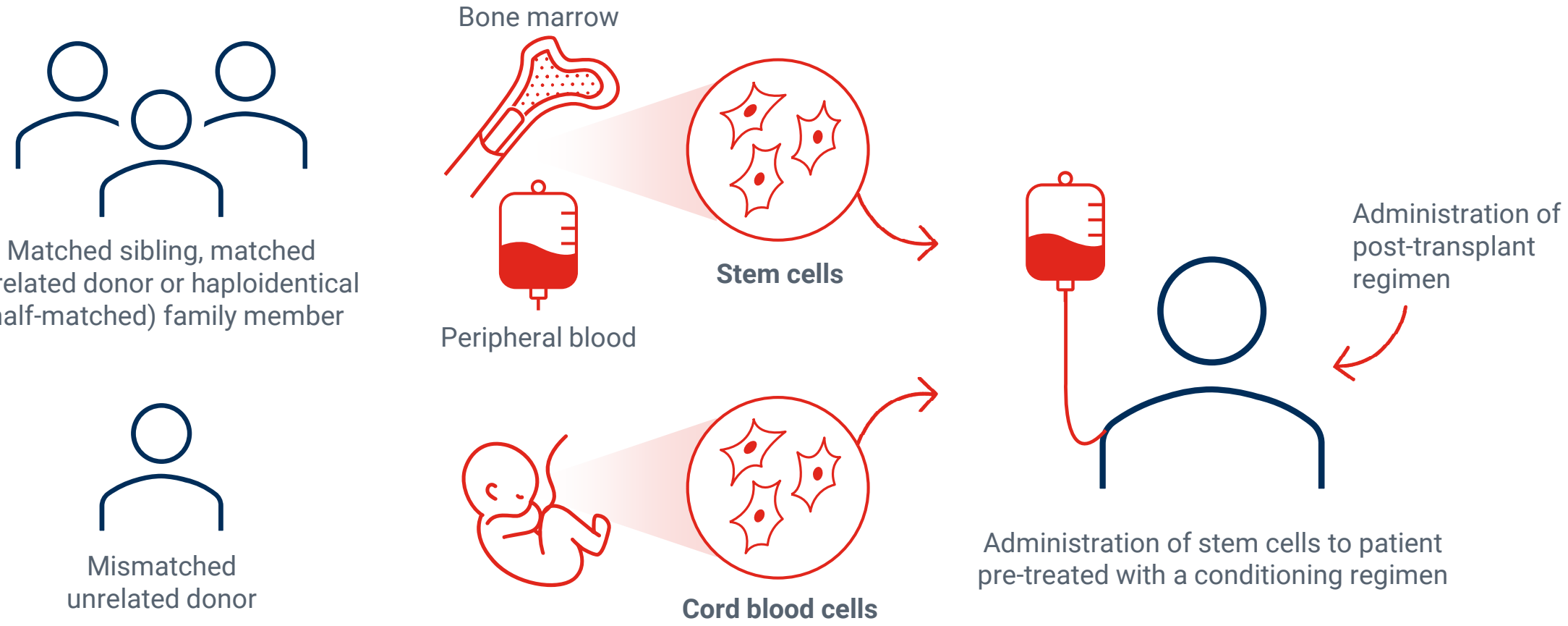
ASCT protocol



ASCT, allogeneic stem cell transplantation.

1. Veldman R, et al. *Discovery Medicine* 2003;16:179–86; 2. Dessie G, et al. *Stem Cells and Cloning: Advances and Applications* 2020;13:67–77;
3. Craddock C, *Hematology* 2018:177 –84.

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Outcomes of ASCT: Efficacy

- Many factors can affect efficacy of treatment at all stages of the procedure (pre- to post-transplant)[1–4]

ASCT, allogeneic stem cell transplant; CR, complete remission; MR, molecular response; NRM, non-relapse mortality.

1. Yassine et al. *Hematology/Oncology and Stem Cell Therapy* 2021; 2. Barrett A, and Ito S. *Blood* 2015;125:3230–35; 3. Hsieh Y, et al. *Leukemia* 2021;35:1229–42; 4. Lübking A, et al. *Bone Marrow Transplantation* 2019;54:1764–74.

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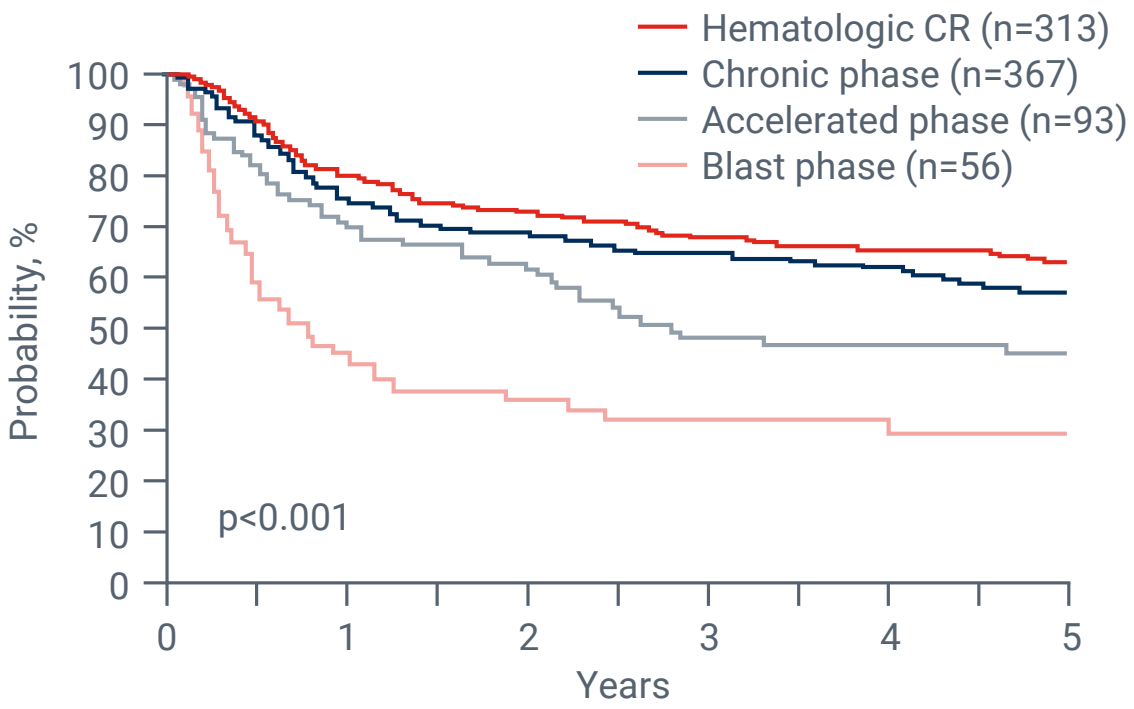
Outcomes of ASCT: Efficacy

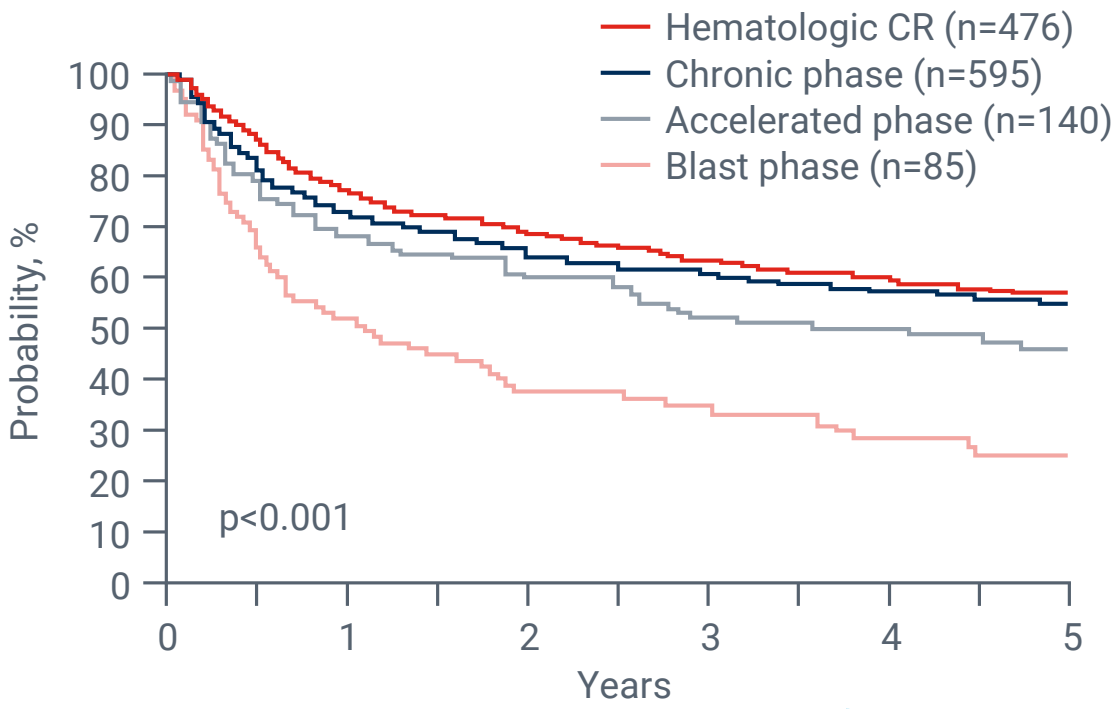
- ASCT has been associated with improved long-term efficacy outcomes in early disease stages[1,2]

Survival after HCT for CML in the US, 2008-2018

Matched related donor



Unrelated donor



ASCT, allogeneic stem cell transplant; CML, chronic myeloid leukemia; HCT; hematopoietic cell transplant; TKI, tyrosine kinase inhibitor

1. Auletta J, et al. Current use and outcome of hematopoietic stem cell transplantation: CIBMTR US summary slides, 2021;
2. Niederwieser C, et al. *Bone Marrow Transplantation* 2021;56:2834–41.

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A summary of clinical trials assessing ASCT outcomes

Study[1]	Registry	Interval	N	Median age	Conditioning	Donor	1-year survival, %	5-year survival, %	10-year survival, %
Millot et al.[2]	SGFMTC	1982–1998	42	14	MA	REL	87	73	73
Cwynarski et al.[3]	EBMT	1985–2001	156	14	NR	REL	78	72	70
Arora et al.[4]	CIBMTR	1988–2003	3514	36	MA	REL	74	63	60
Arora et al.[4]	CIBMTR	1988–2003	531	37	MA	UNR	70	55	50
Radich et al.[5]	Seattle	1995–2000	131	43	MA	REL	91	NA	NA
Gratwohl et al.[6]	German Study III	1997–2004	151	38	MA	REL	90	78	76
Gratwohl et al.[6]	German Study III	1997–2004	148	41	MA	UNR	97	76	76
Bacher et al.[7]	German Registry	1998–2004	1084	40	MA 62%	REL 61%	67	64	64
Ohashi et al.[8]	Japanese Registry	2000–2009	531	40	MA 89%	UNR 51%	87	85	78
Chaudury et al.[9]	CIBMTR	2001–2010	224	24	MA	REL	90	83	NA
Chaudury et al.[9]	CIBMTR	2001–2010	225	24	MA	UNR	80	68	NA
Lee et al.[10]	Korean	2001–2012	47	32	MA 77%	UNR 43%	88	NA	NA
Lee et al.[10]	Korean	2001–2012	50	33	MA 48%	UNR 42%	90	NA	NA
Koenecke et al.[11]	EBMT	2002–2005	193	31	MA	REL	90	85	84
Saussele et al.[12]	German Study IV	2003–2008	19	35	MA 79%	REL 53%	95	NA	NA
Saussele et al.[12]	German Study IV	2003–2008	37	38	MA 65%	UNR 70%	95	NA	NA

CIBMTR, Center for International Blood and Marrow Transplantation; EBMT, European Group for Marrow and Blood Transplantation; MA, myeloablative; NR, not reported; REL, related donor; SGFMTC, Société Française de Greffe de Moelle et de Thérapie Cellulaire; UNR, unrelated donor.

1. Baccarani, M, et al. *Leukemia* 2022;36:1227–36; 2. Millot F, et al. *Bone Marrow Transplantation* 2003;32:993-999; 3. Cwynarski K, et al. *Blood* 2003;102:1224-1231; 4. Arora M, et al. *Journal of Clinical Oncology* 2009;27:1644-1652; 5. Radich J, et al. *Blood* 2003;102:31–35; 6. Gratwohl A, et al. *Leukemia*, 2015;30:562–69; 7. Bacher U, et al. *Annals of Hematology* 2009;88:1237–1247; 8. Ohashi K, et al. *International Journal of Hematology* 2014;100:296-306; 9. Chaudhury S, et al. *Biology of Blood and Marrow Transplantation* 2016;22:1056–64; 10. Lee S, et al. *Hematology* 2013;19:63-72; 11. Koenecke C, et al. *Bone Marrow Transplantation* 2016 51;1259-61; 12. Saussele, S, et al. *Blood* 2010;115:1880–85.

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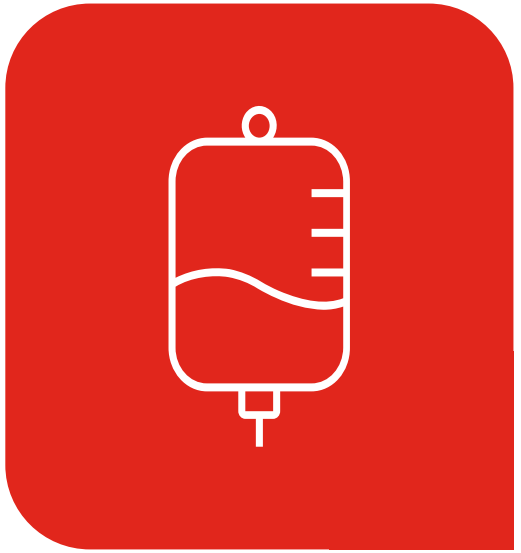
Clinical trials assessing ASCT outcomes

- Given the low number of ASCT for CML performed during the last two decades, recent analyses of large series are lacking.
- The following two studies highlight recent data from the Swedish CML registry and the German CML Study IV from populations having undergone ASCT, and on the role of ASCT in the era of imatinib[1,2]



ASCT, allogeneic stem cell transplantation; AP, accelerated phase; CML, chronic myeloid leukemia.

1. Lübking A, et al. *Bone Marrow Transplantation* 2019;54:1764–74; 2 Saussele, S, et al. *Blood* 2010;115:1880–85.

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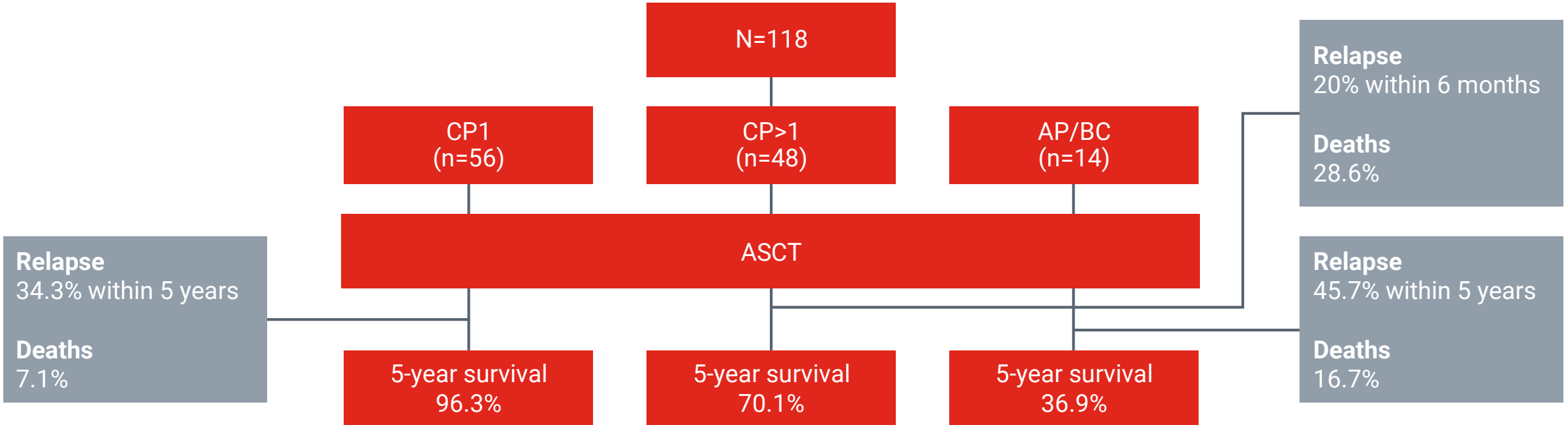
Population-based data from the Swedish cancer registry

- Lübking *et al.* (2019) analyzed the outcomes of patients with CML who underwent ASCT between 2002 and 2017[1]
- OS was dependent on the disease stage, with patients in CP1 achieving a 5-year OS of 96.3%. Patients in advanced disease stages had a 5-year OS of 36.9%[1]



AP, accelerated phase; ASCT, allogeneic stem cell transplantation; BC, blast crisis; CML, chronic myeloid leukemia; CP, chronic phase; OS, overall survival.

1. Lübking A, et al. *Bone Marrow Transplantation* 2019;54:1764–74.

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Population-based data from the Swedish cancer registry

	Phase at time of ASCT		
	CP1	CP>1	AP/BC
Number of patients	56 (47.5%)	48 (40.7%)	14 (11.9%)
Median age	43	45	54
Reason for ASCT			
AP/BC at diagnosis	0	30 (62.5%)	3 (21.4%)
Progression to AP/BC	0	18 (37.5)	9 (64.3%)
T315I mutation	7	0	0
TKI resistance	35 (62.5%)	0	2 (14.3%)
TKI intolerance	5 (8.9%)	0	0
Other reason	9 (16.1%)	0	0

AP, accelerated phase; ASCT, allogeneic stem cell transplantation; BC, blast crisis; CP, chronic phase; TKI, tyrosine kinase inhibitor.

1. Lübking A, et al. *Bone Marrow Transplantation* 2019;54:1764–74.

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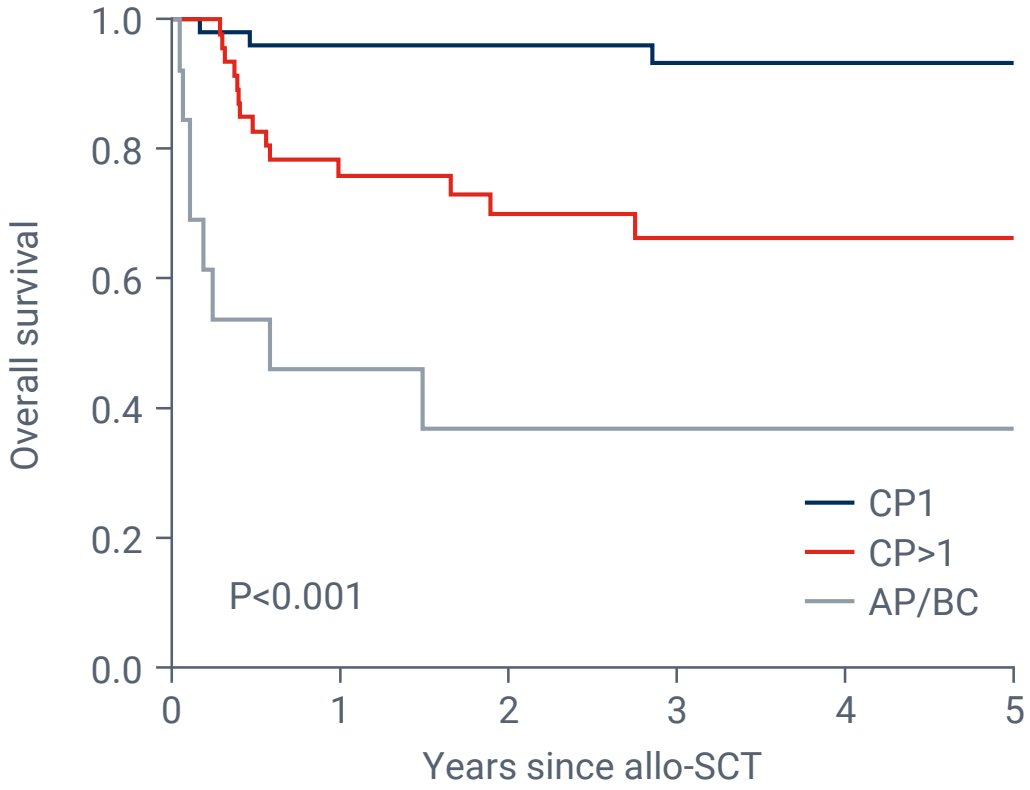
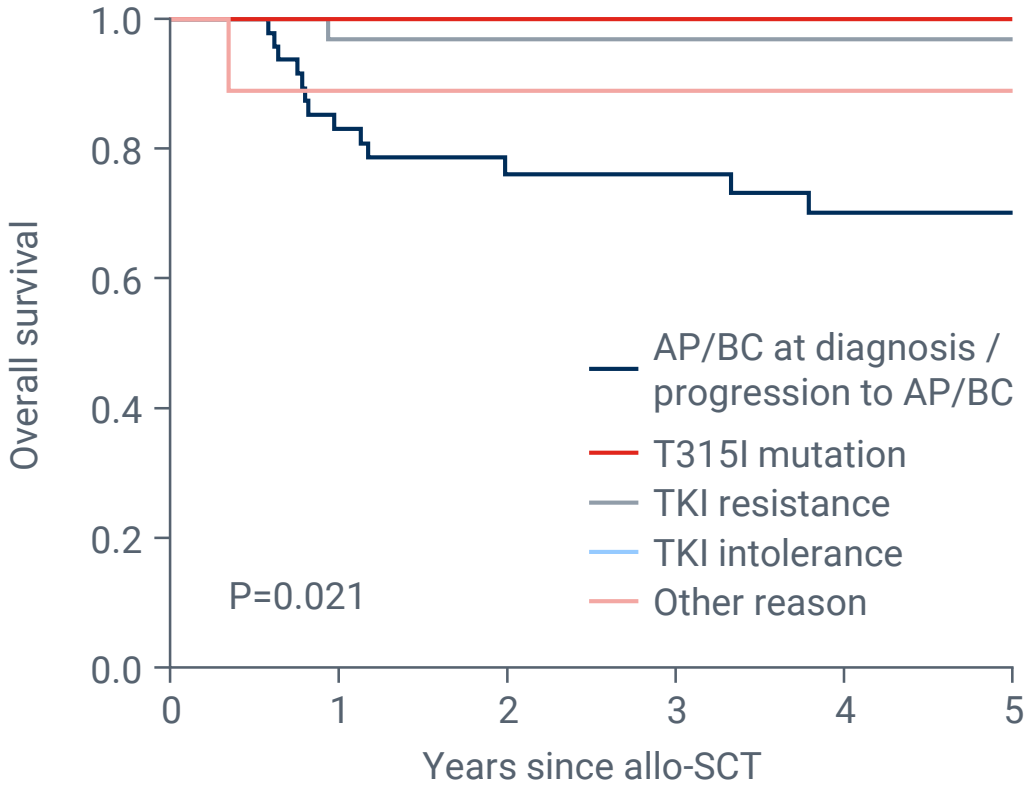
Population-based data from the Swedish cancer registry





AP, accelerated phase; ASCT, allogeneic stem cell transplantation; BC, blast crisis; CP, chronic phase, SCT, stem cell transplant; TKI, tyrosine kinase inhibitor.

1. Lübking A, et al. *Bone Marrow Transplantation* 2019;54:1764–74.

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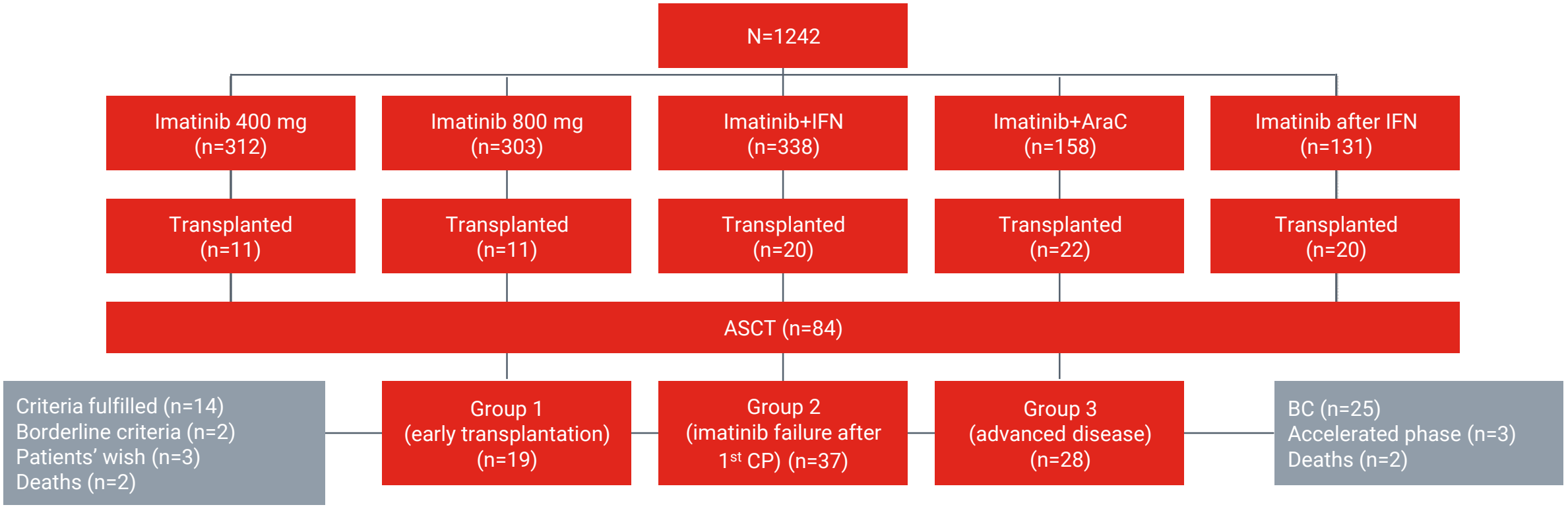
The role of ASCT as second-line therapy after imatinib failure

- Saussele *et al.* (2010) evaluated the role of ASCT as a second-line therapy after imatinib failure (according to ELN guidelines)[1]
- Three-year survival probability post-ASCT in Groups 1, 2 and 3 were 91%, 94.1%, and 59%, respectively, and cumulative TRM was 8%[1]



AraC, cytarabine; ASCT, allogeneic stem cell transplantation; BC, blast crisis; CP, chronic phase; ELN, European LeukeimiaNet; IFN, interferon; TRM, transplantation-related mortality.

1. Saussele, S, et al. *Blood* 2010;115:1880–85.

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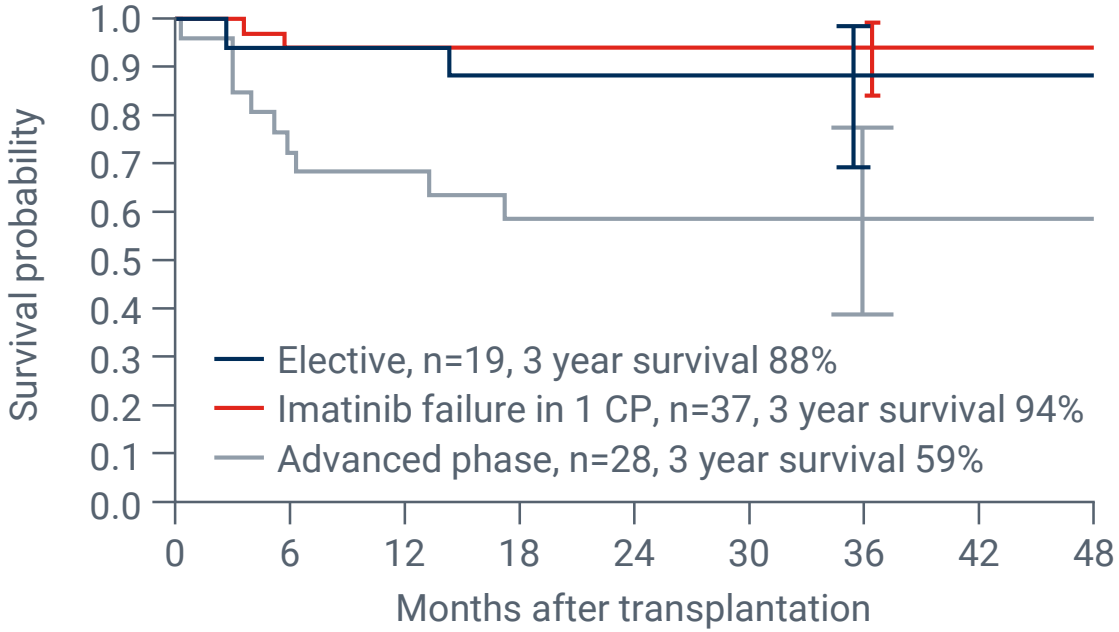
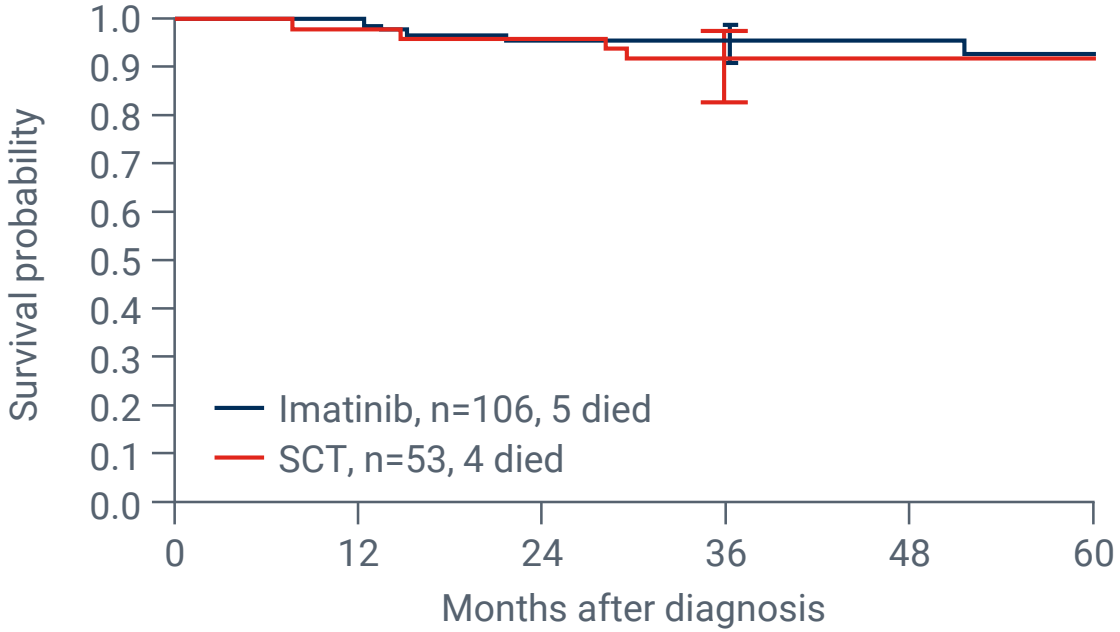
The role of ASCT as second-line therapy after imatinib failure

- Matched pair analyses showed that at 3 years, survival after diagnosis of 53 patients who underwent ASCT was not different from that of 106 matched patients who did not (91.9% [CI: 82.9–97.8%] vs 95.9% [CI: 91.1–98.9%], respectively)
- Complete molecular remission, however, was achieved in 52 transplanted patients (88%), highlighting the curative potential of this treatment approach[1]
- Consistent with previous studies, the best long-term survival results in blast crisis are achieved by ASCT[1]





ASCT, allogeneic stem cell transplantation; CP; chronic phase; SCT, stem cell transplant.

1. Saussele, S, et al. *Blood* 2010;115:1880–85.

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Outcomes of ASCT: Safety

- The most commonly reported risks of ASCT include GvHD, relapse, and infection[1]
- Complications as a result of ASCT may present at any stage post-transplant. These are classed as delayed (3 months to 2 years), late (2 years to 10 years) and very late (>10 years)[2]
- Many of the long-term side effects can be attributed to the impact of GvHD, but may also depend on the intensity of the conditioning regimen and immunosuppression[2]

ASCT, allogeneic stem cell transplant; GvHD, graft versus host disease.

1. Craddock C. *Hematology* 2018:177–184; 2. Mohty B, and Mohty M. *Blood Cancer Journal* 2011;1:e16-e16.

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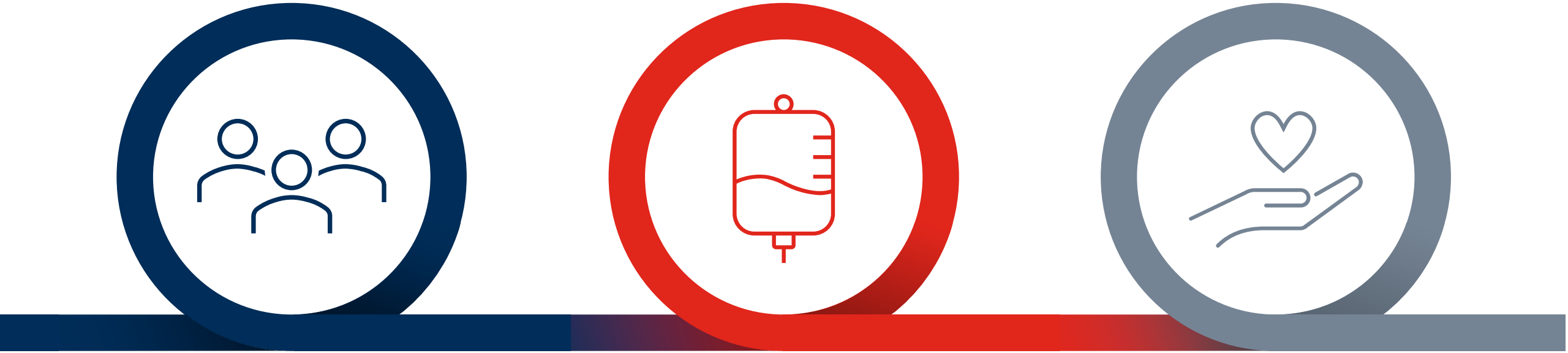
Covariates affecting ASCT outcome: Safety & efficacy



Pre-transplant

- EBMT risk score[1-3]
- Comorbidities (such as organ dysfunction)[2,4]

Transplant

- Stem cell source[2]
- Pre-transplant conditioning regimen (MAC vs. RIC)[3]

Post-transplant

- GvHD[3]
- Relapse[3]
- Transplant toxicity/infection[3]
- Post-transplant regime (cyclophosphamide)[3]
- Optimisation of GVL effect[3]

ASCT, allogeneic stem cell transplant; EBMT, European Society for Blood and Marrow Transplantation; GvHD, graft versus host disease; GVL, graft versus leukemia; MAC, myeloablative conditioning; RIC, reduced intensity conditioning.

1.Rezvani K, et al. *Biology of Blood and Marrow Transplantation* 2012;18:235–40; 2. Veldman R, et al. *Discovery Medicine* 2003;16:179–86; 3. Craddock C. *Hematology* 2018:177–84; 4. Baccarani, M, et al. *Leukemia* 2022;36:1227–36.

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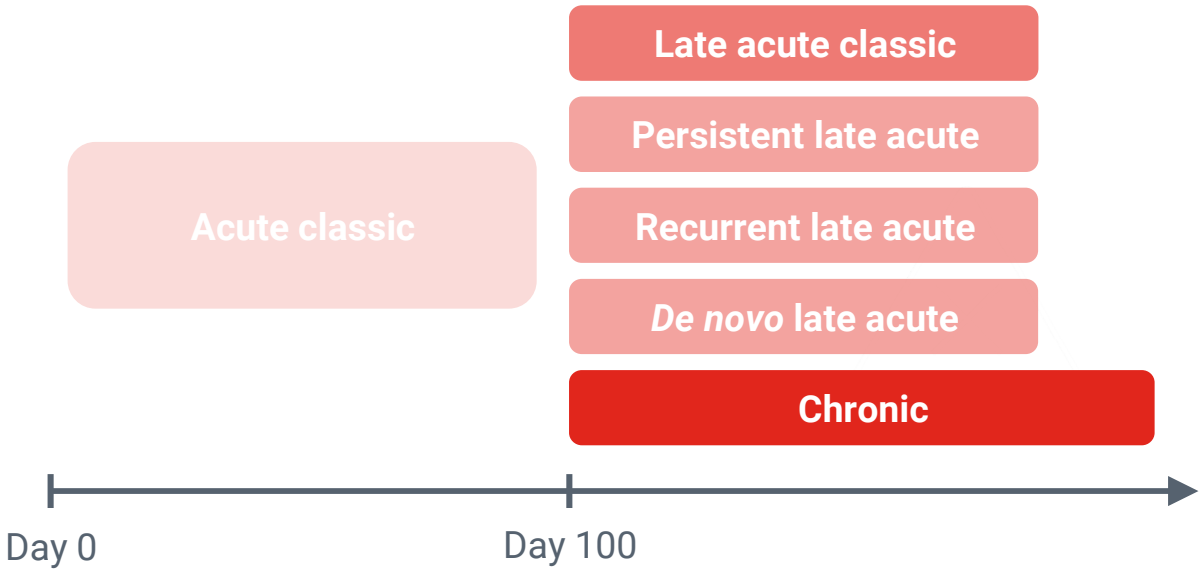
Complications after ASCT

- According to the NIH, GvHD can be classified according to its time of presentation into acute or chronic using a 100 day cutoff period post-transplant. These categories can then be further subdivided according to clinical manifestations[1,2]
- **Acute classic GvHD:** presents within 100 days of the transplantation procedure with classical clinical features of acute GvHD[1]
- **Late acute GvHD:** presents after 100 days of the transplantation procedure with classical clinical features of acute GvHD. This can be further subdivided into **persistent** if it is a continuation of the classic acute GvHD. **Recurrent** if it has been resolved then recurs after the 100 day mark. ***De novo*** if the initial onset occurs after the 100 day mark with no prior acute GvHD[1,2]
- **Chronic GvHD:** presents after 100 days of the transplantation procedure with classical features of chronic GvHD. Furthermore, the diagnosis requires (a) at least one diagnostic manifestation or (b) one distinctive manifestation which is confirmed by biopsy or testing of the organ. These diagnostic manifestations can be found on the skin, in the mouth, genitalia, GI tract and lungs[2]
- Incidence of acute GvHD can be up to 50% in patients receiving the transplant from a matched sibling or even higher in unmatched donors.[1] Incidence of chronic GvHD can range between 6 and 80% and overall mortality can approach 15%[1-3]
- This incidence is variable in function of a number of factors including degree of HLA mismatch, patient age, and intensity of the conditioning regimen[4]



GI, gastrointestinal; GvHD, graft versus host disease; HLA, human leukocyte antigen; NIH, National institutes of health.

1. Vaillant A, et al. *Graft Versus Host Disease* 2021 [Accessed 5 May 2022]; 2. Lee S. *Blood* 2017;129:30–37; 3. Ramachandran V, et al. *Dermatologic Clinics* 2019;37:569–82; 4. Flowers M, et al. *Blood* 2011;117:3214–19.

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Complications after ASCT

Organ/site[1]	Acute GvHD	Chronic GvHD
Skin	Erythema Maculopapular rash Pruritus	Poikiloderma Lichen planus-like features Sclerotic features Morphea-like features Lichen sclerous-like features
Mouth	Gingivitis Mucositis Erythema Pain	Lichen-type features Hyperkaratotic plaques Restriction of mouth opening from sclerosis
Genitalia		Lichen planus-like features Vaginal scarring or stenosis
GI tract	Anorexia Nausea Vomiting Diarrhea Weight loss Failure to thrive (infants and children)	Esophageal web Strictures or stenosis in the upper to mid third of the esophagus
Liver	Total bilirubin, alkaline phosphatases >2 × upper limit of normal ALT or AST>2 × upper limit of normal	
Kidney		Chronic kidney disease
Lung		Bronchiolitis obliterans, bronchiolitis obliterans-organizing pneumonia, idiopathic pneumonia
Muscle, joints		Fascilitis Joint stiffness or contractures secondary to sclerosis
Other		Infections due to abnormal immune reconstitution, higher incidence of diabetes and hypertension, secondary cancers, relapse

ALT, alanine aminotransferase; ASCT, allogeneic stem cell transplant; AST, aspartate aminotransferase; GI, gastrointestinal; GvHD, graft versus host disease.

1. Filipovich et al. *Biology of Blood and Marrow Transplantation* 2005; 11:945-55.

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Summary

- Whilst ASCT no longer represents the primary treatment option, it still remains a salvage therapy for some patients
- The primary aims of ASCT are to improve survival rates in patients with CML
- ASCT is a treatment option for patients who fail to respond to TKIs as stipulated by specific guidelines, have advanced disease or a low EBMT risk score
- Efficacy of ASCT can be affected at all stages of the procedure by a variety of factors
- Complications post-transplant are mainly down to manifestations of GvHD
- Studies have shown ASCT to be an effective second-line strategy for prolonging OS, notably in patients with early disease who have failed first-line therapies

ASCT, allogeneic stem cell transplantation; CML, chronic myeloid leukemia; EBMT, European group for blood and bone marrow transplantation; GvHD, graft-versus-host disease; OS, overall survival; TKI, tyrosine kinase inhibitor.

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