HLA-Haploidentical Hematopoietic Cell Transplantation (HCT) using Post-Transplantation Cyclophosphamide (PTCy)

Christopher Kanakry, M.D.

Lasker Clinical Research Scholar

Experimental Transplantation and Immunology Branch

Center for Cancer Research, National Cancer Institute, NIH

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Limitations in Donor Options

- Allogeneic HCT is a life-saving treatment for otherwise incurable hematologic diseases
- Only ~30% of patients have an HLA-matched-sibling donor (MSD)
- HLA-matched-unrelated donor (MUD) options vary depending on ethnicity
- HLA-haploidentical related donors, umbilical cord blood (UCB), or HLA-mismatched-unrelated donors are options for the rest of patients
- Nearly all patients have HLA-haploidentical donors

U.S. Racial and Ethnic Group	Likelihood of Identifying an Adult Donor*
	8/8 HLA Match
White European	75
Middle Eastern or North African	46
African American	19
African	18
Black South or Central American	16
Black Caribbean	19
Chinese	41
Korean	40
South Asian	33
Japanese	37
Filipino	40
Southeast Asian	27
Vietnamese	42
Hawaiian or Pacific Islander	27
Mexican	37
Hispanic South or Central American	34
Hispanic Caribbean	40
Native North American	52
Native South or Central American	49
Native Caribbean	32
Native Alaskan	36

Gragert et al. *NEJM*. 2014.

Historically (1985-1991) Poor Outcomes with HLA-Haploidentical HCT: CIBMTR Data

Type of Donor	Outcome		
	Graft Failure	Grade III to IV Acute GVHD	Chronic GVHD
HLA-Identical Sibling			
No.	1,176	1,176	1,025
Probability (± SE) (%)	1 ± 0.3	13 ± 1	42 ± 2
1-Antigen mismatched related			
No.	232	223	164
Probability (± SE) (%)	9 ± 2	27 ± 3	52 ± 4
*P**	< .001	< .001	< .001
2-Antigen mismatched related			
No.	93	86	57
Probability (± SE) (%)	16 ± 4	36 ± 6	60 ± 9
*P**	< .001	< .001	.02

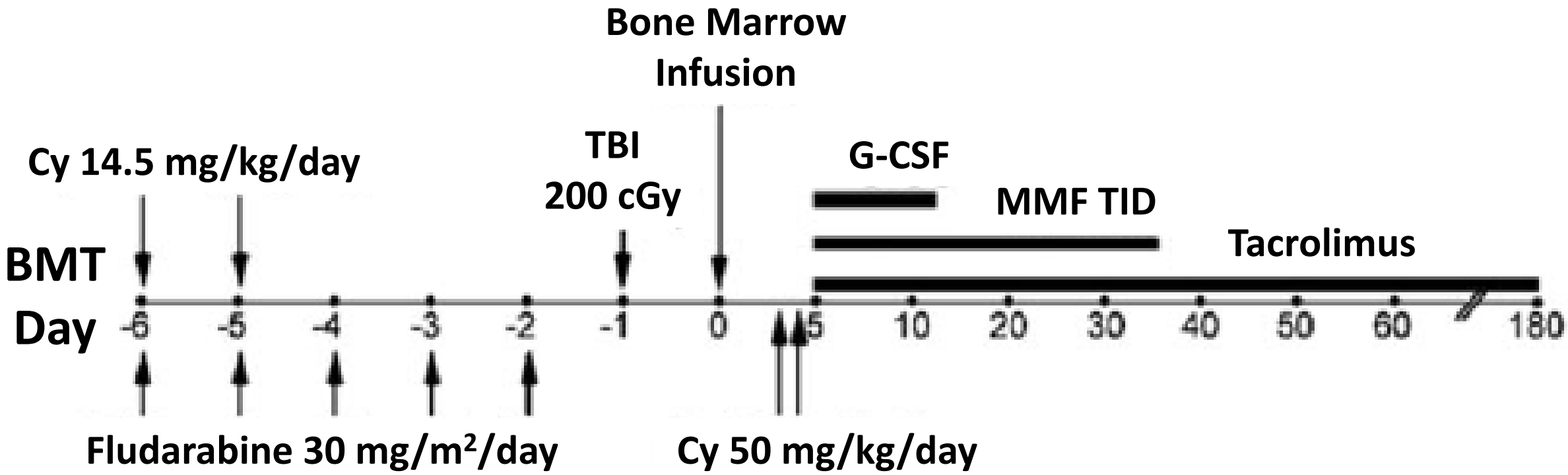
Adapted from Szydlo et al. *JCO.* 1997.

Historically (1985-1991) Poor Outcomes with HLA-Haploidentical HCT: CIBMTR Data

Disease State/Type of Donor	No.	Probability			
		Treatment-Related Mortality %	*P*	Leukemia-Free Survival %	*P*
Early					
HLA-identical sibling	805	21 ± 2	—	66 ± 2	—
1-Antigen mismatched related	104	53 ± 5	< .001	33 ± 5	< .001
2-Antigen mismatched related	24	55 ± 11	< .001	25 ± 10	< .001
Intermediate					
HLA-identical sibling	241	38 ± 3	—	44 ± 4	—
1-Antigen mismatched related	82	50 ± 6	.01	36 ± 6	.06
2-Antigen mismatched related	37	67 ± 10	.002	20 ± 8	.005
Advanced					
HLA-identical sibling	178	54 ± 6	—	12 ± 3	—
1-Antigen mismatched related	52	57 ± 10	.58	15 ± 6	.79
2-Antigen mismatched related	41	66 ± 10	.001	22 ± 8	.26

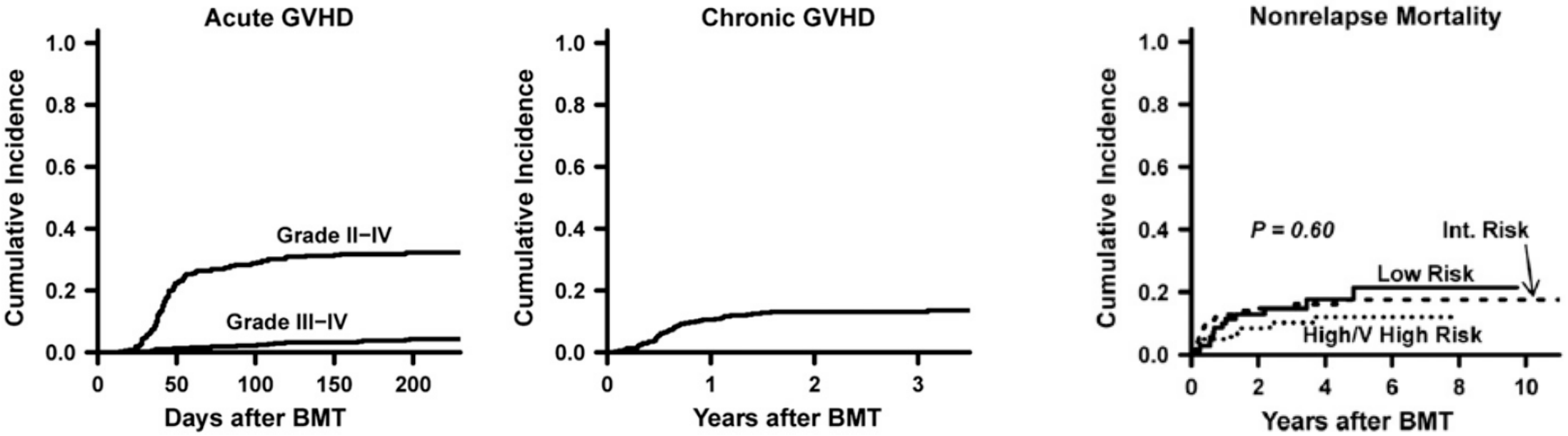
Adapted from Szydlo et al. *JCO.* 1997.

Initial HLA-Haploidentical HCT Platform Using PTCy



Luznik et al. *BBMT*. 2008.

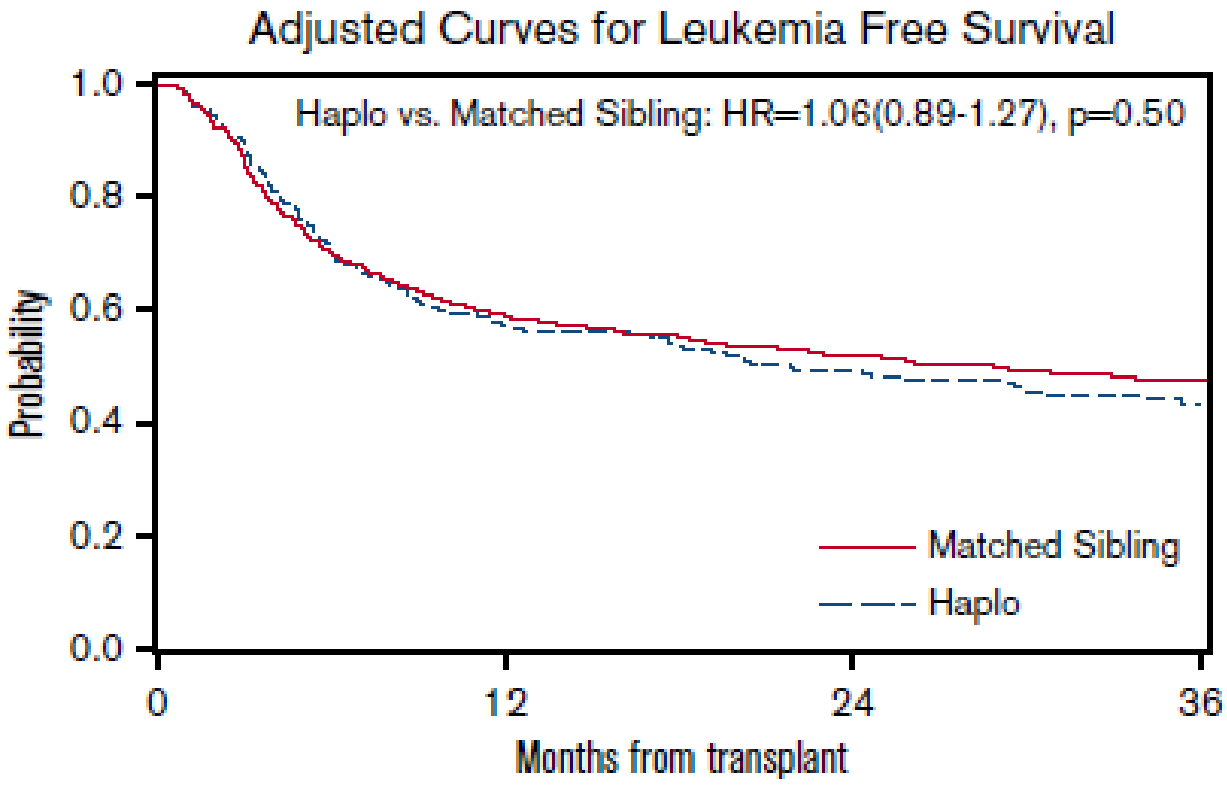
Outcomes Using this Platform for HLA-Haploidentical HCT

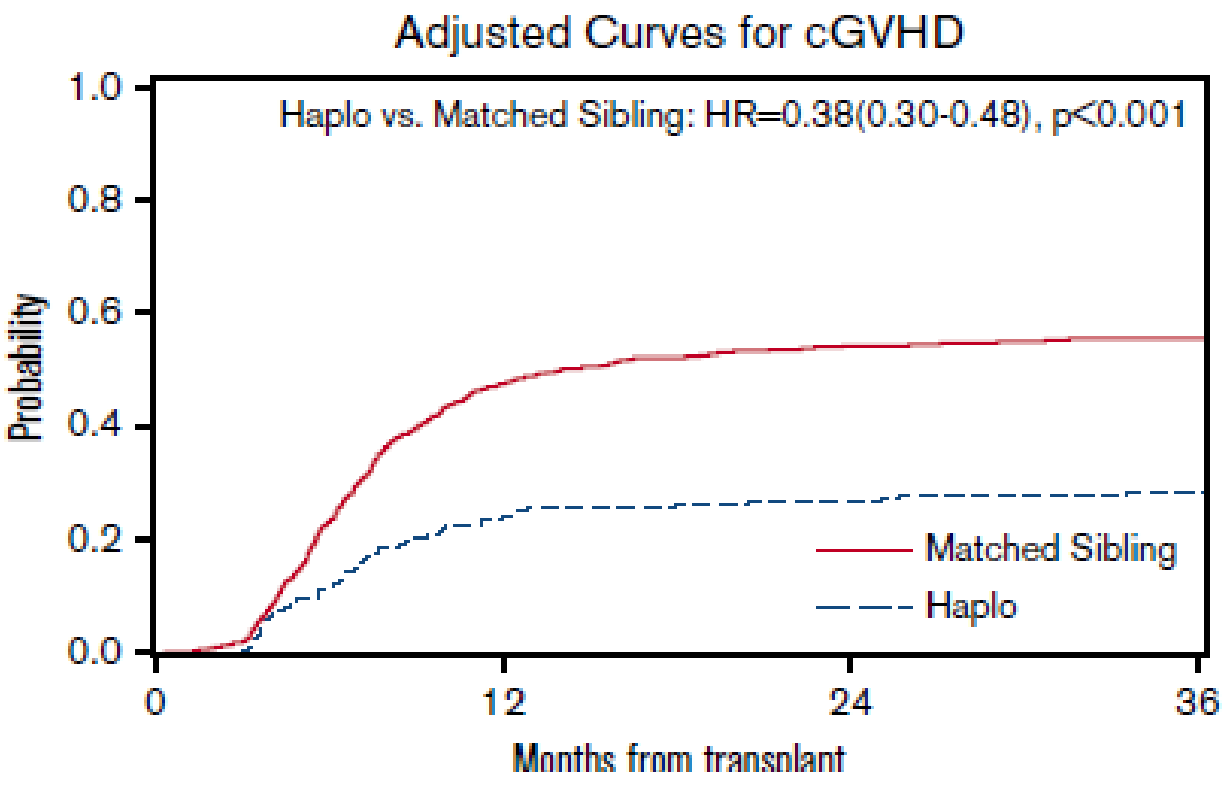


N=372

McCurdy et al. *Blood*. 2015.

Similar Survival but Lower Chronic GVHD for Adults using PTCy-based Haploidentical compared with HLA-matched-sibling donor HCT for AML in CR1





Rashidi et al. *Blood Adv*. 2019.

PTCy Current Dosing is Partly Extrapolated and Partly Empirical

- PTCy was effective at preventing rejection of murine skin allografts[1]
  - Most effective when using Cy 200 mg/kg on day +2 or +3
- PTCy 200 mg/kg on day +2 or +3 decreased GVHD in murine HCT[2]
- When PTCy was translated to clinical HCT, it was given at a "high dose" (50 mg/kg, near the maximal tolerated dose by humans) and on day +3 to space as far away from conditioning as possible
- Second dose empirically added on day +4
  - JHU cohort (two doses, n=40) had lower extensive chronic GVHD (p=0.05) than the FHCRC cohort (one dose, n=28)[3]

[1]Mayumi et al. *Transpl Proc.* 1986; [2]Luznik et al. B*lood*. 2001; [3]Luznik et al. *BBMT*. 2008

Can the Dosing of PTCy Be Optimized?

- PTCy 25 mg/kg/day on days +3 and +4 was superior to lower or higher doses in two murine HCT models[1]
- In our MHC-haploidentical HCT model:
  - The efficacy of PTCy peaks at day +4
  - PTCy 25 mg/kg/day on day +4 was equivalent to days +3/+4

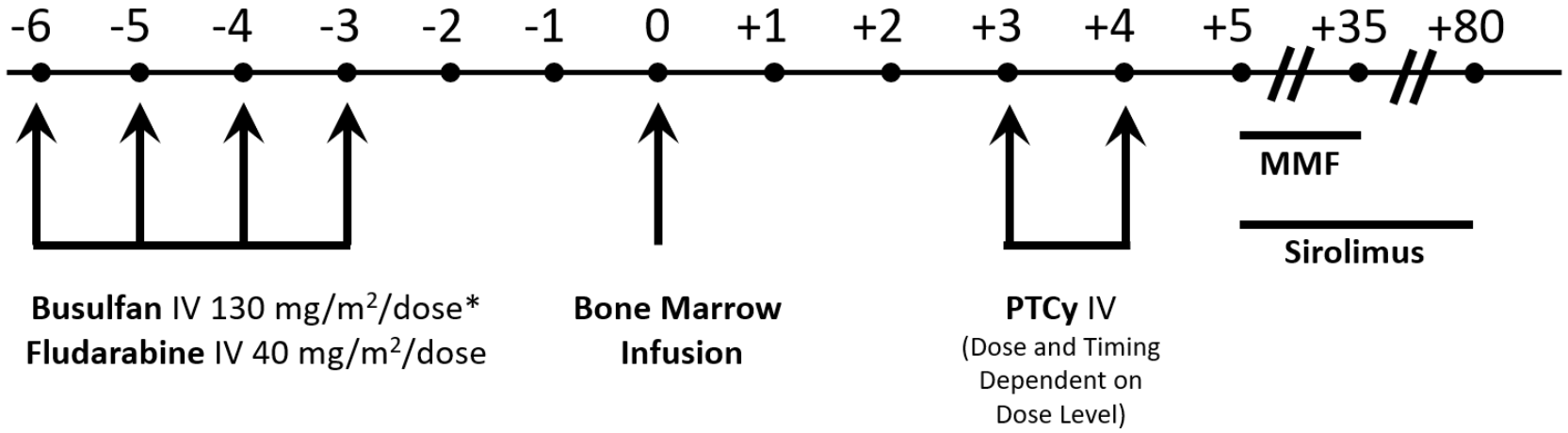
[1]Wachsmuth et al. *JCI*. 2019

Protocol Design

- Primary objective: Determine whether a dose of PTCy 25 mg/kg on days +3 and +4 and subsequently on day +4 only can maintain adequate protection against grade III-IV acute GVHD
- PTCy dose de-escalation:
  - Dose level 1: standard 50 mg/kg on days +3/+4 (5 patients only to get comparator samples)
  - Dose level 2: 25 mg/kg/day on days +3/+4
  - Dose level 3: 25 mg/kg on day +4 only
- Expansion cohort at lowest dose that does not result in excess DLTs.

Protocol Design

- Platform: Myeloablative conditioning, HLA-haploidentical bone marrow allografts, PTCy/MMF/sirolimus for GVHD prophylaxis



- Eligibility is 15-65 yo patients with adequate end-organ function and performance status and hematologic malignancy with standard indication for allogeneic HCT

Potential Benefits of Optimizing the Timing and Dosing of PTCy

- Decrease toxicity
- Better prevention of both acute and chronic GVHD
- Decrease adjunct immunosuppression required
  - This will better allow integration of other immunotherapeutic strategies targeting relapse
- More rapid engraftment/decreased duration of neutropenia
- Improved immune reconstitution and thus potentially infectious immunity

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Disease Eligibility

Histologically or cytologically confirmed hematologic malignancy with standard indication for allogeneic HCT including one of the following:

- Acute myeloid leukemia (AML) of intermediate or adverse risk disease by the 2017 European LeukemiaNet criteria[1] in first morphologic complete remission
- AML of any risk in second or subsequent morphologic complete remission
- B-cell acute lymphoblastic leukemia in first or subsequent complete remission[2,3]
- T-cell acute lymphoblastic leukemia with minimal residual disease detected after first line therapy and/or adverse genetics[4]
- Myelodysplastic syndrome of intermediate or higher score by the Revised International Prognostic Scoring System (IPSS-R)[5]
- Primary myelofibrosis of intermediate-2 or higher risk by the DIPSS[6]
- Chronic myelomonocytic leukemia
- Chronic myelogenous leukemia resistant to or intolerant of ≥3 tyrosine kinase inhibitors or with prior history of accelerated phase or blast crisis
- B-cell lymphoma including Hodgkin lymphoma that has relapsed within 1 year of completion of primary treatment[7]
- Chronic lymphocytic leukemia with 17p deletion and/or unmutated or IgH_V[8] or refractory or intolerant of both BTK and PI3K inhibitors
- Mature T or NK neoplasms as defined in the WHO guidelines of sufficient type and severity for allogeneic HCT based on the Prognostic Index for T-cell lymphoma (PIT) score of low-intermediate risk or higher or on recently published clinical practice guidelines
- Hematologic malignancy of dendritic cell or histiocytic cell type
- Multiple myeloma, stage III[10], relapsing after therapy with both a proteasome inhibitor and an immunomodulatory drug (IMiD)