Allogeneic hematopoietic cell transplantation outcomes in patients with Richter's transformation

Approximately 2-10% of chronic lymphocytic leukemia (CLL) cases develop into Richter's transformation (RT), a more aggressive disease typically manifesting as diffuse large B-cell lymphoma (DLBCL).[1] Targeted therapies such as ibrutinib are now commonly used to treat CLL but the transformation rate remains comparable to the chemoimmunotherapy era.[2] Moreover, these targeted therapies are often used to treat RT despite limited efficacy,[1,3] and prognosis for these patients is poor.[4-6] The treatment of RT therefore remains challenging in the current era of targeted therapy.

Graft-*versus*-leukemia activity after allogeneic hematopoietic cell transplantation (alloHCT) is evident in patients with CLL where durable remissions can be achieved in all genetically defined high-risk subsets.[7,8] Indeed, several small studies have reported benefit from alloHCT in RT.[9-11] In order to better understand the therapeutic value of alloHCT in the modern era, we report alloHCT outcomes for 28 consecutive patients with RT who received chemoimmunotherapy and/or targeted therapy prior to alloHCT.

The Blood and Marrow Transplant data repository of the Dana-Farber Cancer Institute was queried to identify all patients aged ≥18 years who underwent alloHCT for RT between January 1, 2010 and May 31, 2019. After obtaining Institutional Review Board approval in accordance with the Declaration of Helsinki, a retrospective chart review was performed to confirm the diagnosis of CLL and transformation to RT and 28 patients were identified. Clinical characteristics of these patients are summarized in the *Online Supplementary Table S1*. Median age was 61 years (range: 41-73 years) and 24 (85.7%) were male. Twenty-six patients received reduced intensity conditioning (RIC) HCT. The histologic diagnosis at alloHCT was DLBCL (n=27) and Hodgkin lymphoma (n=1). Median time from CLL diagnosis to RT was 4.5 years (range: 0- 24.4 years). Median time from RT to alloHCT was 0.6 years (range: 0.2-3.8 years). Twenty-six patients (92.8%) were in complete remission (CR) or partial remission (PR) at the time of alloHCT. Positron emission tomography (PET) scan was available for 23 patients and seven (30%) of these 23 patients were PET positive. Of note, since RT is a high risk disease, our current practice is to offer alloHCT only to those patients in at least PR. Median number of total therapies for CLL and RT combined prior to alloHCT was three (range: 1-7): one (range: 0-4) for CLL and two (range: 1-7) for RT. Nine patients received targeted therapies (4 for CLL and 5 for RT) in addition to chemoimmunotherapies before alloHCT. No patient received CAR-T cell therapy. All prior and post-transplant therapies are listed in *Online Supplementary Table S2*.

Time from CLL diagnosis to RT and alloHCT, relapse, post HCT therapy, and duration of overall survival (OS) for the entire cohort are depicted in Figure 1 along with selected clinical features such as age, prior targeted therapy, total number of prior therapies, complex karyotype (defined as ≥5 abnormalities),[12] HCT comorbidity index, disease status, donor type, bulky disease, high lactate dehydrogenase (LDH) and/or low platelet counts ($<100x10^9$/L), and a PET scan result at transplant and occurrence of grade 2-4 acute graft-*versus*-host disease (GvHD). Strikingly, the cohort is dichotomized into a group of long survivors and a group that experienced early deaths. In the first group (subjects 15-28), all patients remain alive (4-year overall survival [OS] 100%) with median follow-up 4.9 years (range: 2.2-7.7 years). In the second group (subjects 1-14), 11 of 14 died within 1 year (1-year OS 21%). Remarkably, two of three patients aged >70 years survived over 5 years. Subject 27 was 73 years old at the time of alloHCT, relapsed 11 months after alloHCT, and subsequently received post-transplant therapy (CHOP) and donor lymphocyte infusion from his brother. This patient remains alive 7.3 years after alloHCT. Subject 22 was also 73 years old at the time of alloHCT, had del(17p) and developed RT while on ibrutinib. This subject subsequently responded to R-EPOCH prior to alloHCT and remains alive in remission 5.2 years after alloHCT.

For the entire cohort, eight relapses (7 RT and 1 CLL) and 13 deaths have occurred: five from disease progression, six from infection and two from GvHD. Of the eight non-relapse deaths, six died within 1 year and two within 2 years of alloHCT. Median follow-up among sur-

Table 1. Kaplan-Meier estimates for overall and progression-free survival and estimates of cumulative incidences of non-relapse mortality, relapse, acute graft-*versus*-host disease and chronic graft-*versus*-host disease in the competing risks framework.

	All (N=28) (95% CI)	High Risk (N=9) (95% CI)	Standard Risk (N=19) (95% CI)	*P*	Age ≥65 (N=10) (95% CI)	Age<65 (N=18) (95% CI)	*P*
4-yr OS	53% (33-70)	11%* (0.6-39)	74% (48-88)	<0.0001	40% (12-67)	61% (35-79)	0.16
4-yr PFS	39% (21-56)	0%	58% (33-76)	<0.0001	10% (0.6-36)	55% (30-74)	0.006
4-yr NRM	29% (13-47)	33%* (5-67)	21% (6-42)	0.21	20% (2-50)	34% (13-56)	0.58
4-yr Relapse	32% (16-50)	56% (16-83)	21% (6-42)	0.054	70% (25-91)	11% (2-30)	0.007
6 mo. Grade 2-4 aGvHD	36% (19-54)	56% (17-82)	21% (6-42)	0.013			
6 mo. Grade 2-4 aGvHD	18% (6-34)	37% (6-71)	11% (1.7-29)	0.12			
2 yr cGvHD	52% (30-70)	25% (2.5-60)	61% (33-80)	0.43			
	OS HR (95% CI)	PFS HR (95% CI)	NRM sHR (95% CI)	Relapse sHR (95% CI)			
Grade II-IV aGvHD	3.94 (1.36-12.4)	2.05(0.8-5.09)	7.36 (1.59-34)	0.53 (0.1-2.81)			
P	0.016	0.13	0.01	0.45			

Log-rank was used for comparisons of overall survival (OS) and progression-free survival (PFS). Gray test was used for comparisons of non-relapse mortality (NRM), relapse and graft-*versus*-host disease (GvHD). The table presents results of univariable analysis for the effect of grade 2-4 acute GvHD (aGvHD) on outcomes. Cox model was used for OS and PFS and cause-specific Cox model was used for NRM and relapse. Occurrence of grade 2-4 aGvHD was treated as a time dependent variable. HR: hazard ratio; CI: confidence interval; mo: months; yr: years; cGvHD: chronic GvHD. *3-year estimate as the last patient in this cohort was censored at 36.3 months.

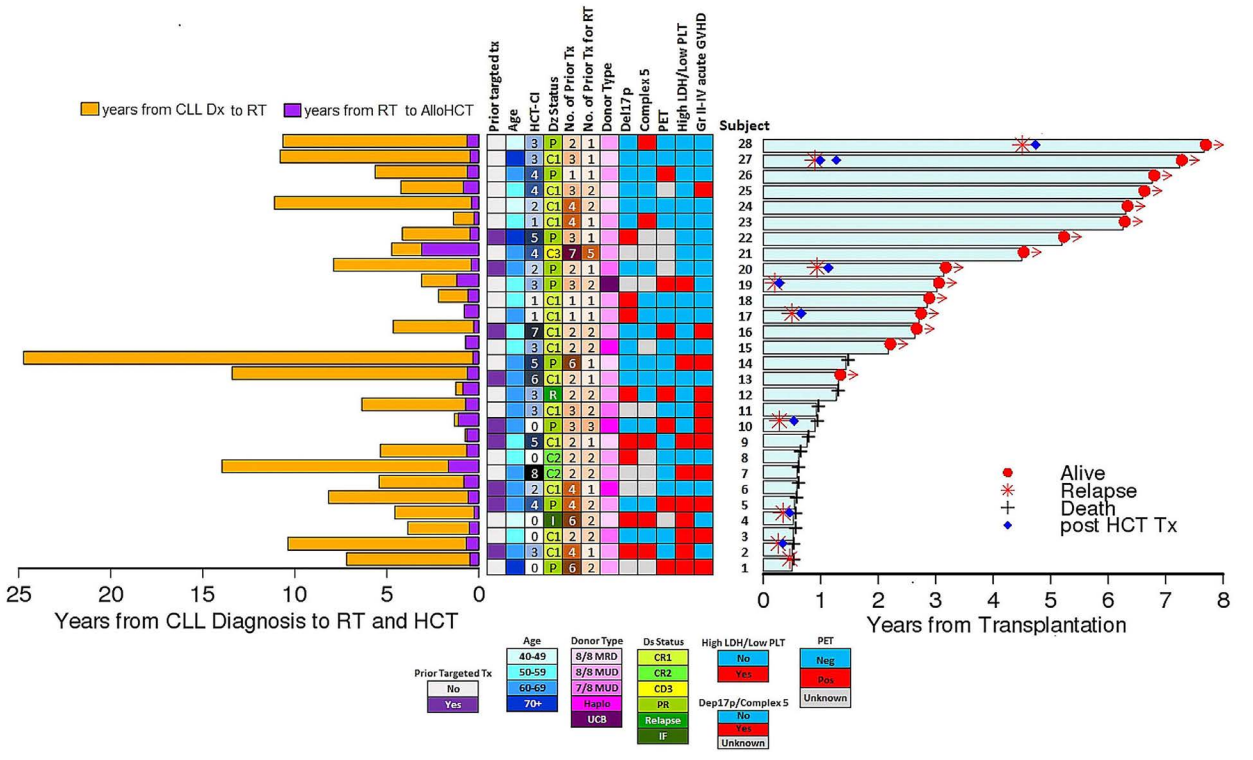

Figure 1. Swimmer plot. Right panel: time from allogeneic hematopoietic cell transplantation (alloHCT) to post transplant events. Left panel: time from chronic lymphocytic leukemia (CLL) diagnosis to Richter's transformation (RT) and alloHCT. Middle panel: selected risk features. HCT-CI: HCT comorbidity index; Complex 5: complex karyotype defined as ≥5 abnormalities.[12] High lactate dehydrogenase (LDH) is defined as LDH >205 U/L. Low PLT: platelet count <100x10^9/L.

vivors was 54 months (range: 16-92 month); median OS was not reached and median PFS was 11.2 months. Four-year OS, progression-free survival (PFS), cumulative incidence of non-relapse mortality (NRM) and relapse were 53%, 39%, 29% and 32%, respectively. (Figure 2A and B). The cumulative incidence of grade 2-4 and grade 3-4 acute GvHD at 6 months were 36% and 18%, respectively (Table 1).

As for risk factors, all four patients with low platelet counts (subjects 1, 2, 4 and 5) and six of seven patients with high LDH died within 17 months of alloHCT (subjects 3, 4, 5, 7, 9 and 14) (Figure 1). Due to the small number of patients with high LDH and low platelet counts, these two factors were combined and considered 'high risk'. Four-year OS was 11% in this high risk group and 74% in the standard risk group (P<0.0001) (Table 1; Figure 2C). In addition, patients who developed grade 2-4 acute GvHD did poorly, with nine of 11 dying within 18 months (hazard ratio [HR] for OS: 3.94, P=0.016) (Figure 1; Table 1). High risk was also associated with poor PFS (4-year PFS 0% *vs.* 58%, P<0.0001) (Table 1; Figure 2D). Age was not a significant risk factor for OS but was significant for PFS (4-year PFS 10% for age ≥65 *vs.* 55% for age <65 years, P=0.006) (Table 1; *Online Supplementary Figure S1A*). Risk factors for NRM included the occurrence of grade 2-4 acute GvHD (HR: 7.08, P=0.017) (Table 1). Risk factors for relapse included age ≥65 years (4-year cumulative incidence 70% *vs.* 11%, P=0.007) and high risk (4-year cumulative incidence 56% vs. 21%, P=0.05). (Table 1; *Online Supplementary Figure S1B and D*). Other factors did not affect outcomes. In particular, remission status (CR *vs.* PR), Eastern Cooperative Oncology Group performance status, HCT comorbidity index, use of targeted therapy prior to alloHCT, number of prior therapies, year of HCT, PET positivity, bulky disease, fluorescence *in situ* hybridization (FISH) abnormalities and complex karyotype did not affect outcomes.

To our knowledge, this is the largest study reporting outcomes of patients with RT who underwent alloHCT in recent years. We report favorable outcomes for these previously treated patients. Importantly, half of these patients have extended OS, reaching a plateau after 1.5 years post transplant. This suggests that some RT patients could be cured with alloHCT.

For factors that are associated with poor outcome, high risk disease (i.e., low platelet counts and/or high LDH) was significantly associated with shorter OS and PFS. Outcome for patients with standard risk at transplant was excellent (4-year OS and PFS: 74% and 58%, respectively) despite the fact that these patients had failed multiple therapies. In contrast, few patients with high risk showed benefit from alloHCT suggesting that LDH and platelet counts together could be a sensitive marker of residual disease, since radiologic remission status based on PET/CT imaging at transplant was not predictive of outcome. In addition to these factors, advanced age was associated with poor outcome. Interestingly, use of prior targeted therapy was not associated with improved outcome. Similarly, year of transplant and number of prior therapies for CLL or for RT did not affect clinical outcome. These findings are very different from CLL patients who undergo alloHCT in the modern era[13] but resemble observations made in alloHCT of *de novo* DLBCL,[14] suggesting that disease control and sensitivity to alloHCT may be most critical for an aggressive disease like RT.

The survival outcome reported in the current study compares favorably to previously published alloHCT series in RT. The European Society for Blood and Marrow Transplantation[10] (n=25, 72% RIC) reported 3-year OS

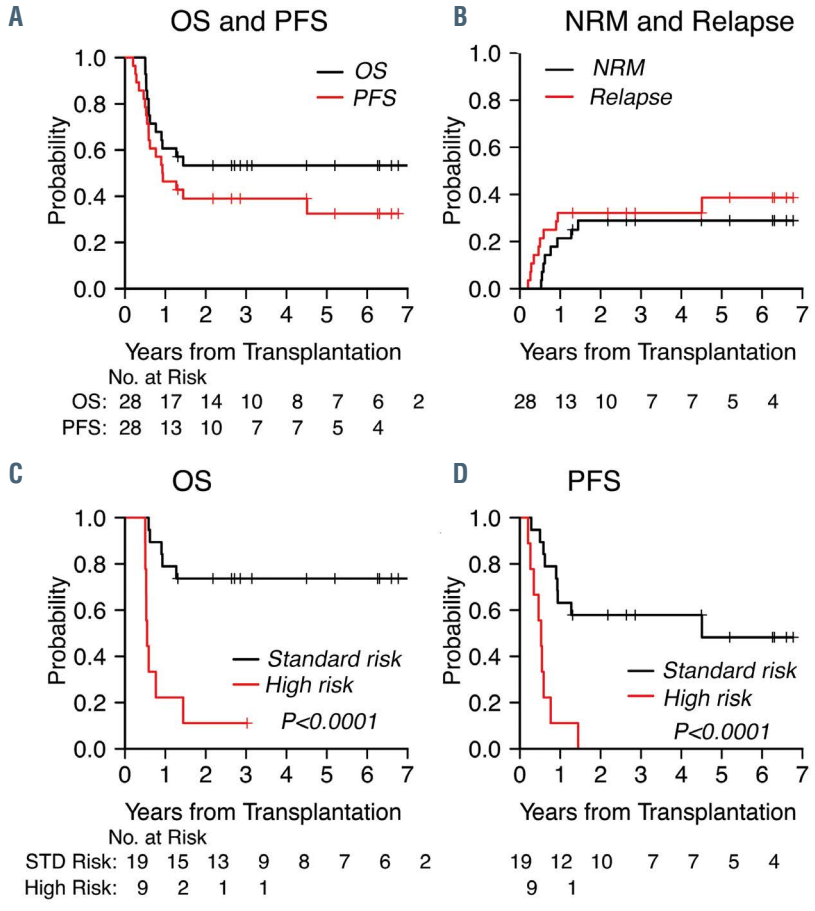

Figure 2. Clinical outcomes. (A) Overall survival (OS) and progression-free survival (PFS) and (B) cumulative incidence of non-relapse mortality (NRM) and relapse for the entire cohort. (C) OS and (D) PFS according to the risk group.

41% among 16 patients who received alloHCT in CR/PR, and 17% for nine patients with progressive disease. In a series of single-center studies, Kharfan-Dabaja *et al.*[11] (n=10, all patients were in CR/PR) reported 4-year OS and PFS 50%; Tsimberidou *et al.*[9] (n=17) reported 3-year OS 75% for seven patients who received alloHCT as postremission therapy and 21% for 13 patients who received allo- or autoHCT as salvage therapy. For patients with RT who do not achieve remission, CAR-T cell therapy is a newer option, with recently reported results in a small series (n=9) with limited follow-up by Kittai *et al.*[15] Further and larger studies with longer follow-up are warranted to evaluate the efficacy of this therapy on its own or as a bridge to alloHCT.

This study has some limitations owing to its single-center retrospective design with a small sample size of 28 patients, which nonetheless is the largest study to date. Another limitation is the absence of data on clonal relationship between RT and CLL. Published literature,[16] however, shows that the majority (~80%) of RT is clonally related to the preceding CLL, particularly in heavily pretreated patients like these, suggesting that most RT patients in this study were clonally related.

With availability of less toxic/reduced induced intensity conditioning regimens, improved human leukocyte antigen typing, and better GvHD prophylaxis strategies, alloHCT has become a viable and safe treatment option for patients with high risk hematologic cancers, even with advanced age. Our study results show that a sizeable proportion of patients with RT in remission can achieve durable remissions, and that alloHCT should be considered as a treatment option for patients with RT who are fit and have controlled disease.

Haesook T. Kim,[1] Peter O. Baker,[2] Erin Parry,[2] Matthew Davids,[2] Edwin P. Alyea,[3] Vincent T. Ho,[2] Corey Cutler,[2] John Koreth,[2] Mahasweta Gooptu,[2] Rizwan Romee,[2] Sarah Nikiforow,[2] Joseph H. Antin,[2] Jerome Ritz,[2] Robert J. Soiffer,[2] Catherine J. Wu[2#] and Jennifer R. Brown[2#]

[1]Department of Data Science, Dana Farber Cancer Institute, Harvard School of Public Health, Boston, MA; [2]Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA and [3]Duke Cancer Institute, Duke Medical School, Durham, NC, USA

[#]CJW and JRB contributed equally as co-senior authors.

Correspondence:

JENNIFER R. BROWN - jennifer_brown@dfci.harvard.edu

HAESOOK T. KIM - htkimc@jimmy.harvard.edu

doi:10.3324/haematol.2021.279033

Received: April 19, 2021.

Accepted: August 17, 2021.

Pre-published: August 26, 2021.

Disclosures: JRB has served as a consultant for Abbvie, Acerta, Astra-Zeneca, Beigene, Catapult, Dynamo Therapeutics, Juno/Celgene, Kite, MEI Pharma, Nextcea, Novartis, Octapharma, Pfizer, Sunesis, TG Therapeutics, Verastem; received honoraria from Janssen and Teva; received research funding from Gilead, Loxo, Sun and Verastem; and served on data safety monitoring committees for Morphosys and Invectys, outside the submitted work. CJW holds equity in BioNTech, Inc, and receives research funding from Pharmacyclics, Inc, outside the submitted work. JR has received research funding from Amgen, Equillium, Kite Pharma and Novartis; and served as a consultant for Avrobio, Celgene, Clade Therapeutics, Garuda

Therapeutics, Immunitas Therapeutics, LifeVault Bio, Novartis, Rheos Medicines, Talaris Therapeutics and TScan Therapeutics, outside the submitted work. JK has served as a consultant for Amgen, Equillium, Cugene, and Moderna and advisory board for therakos; and received funding from BMS, Miltenyi, Clinigen, and Regeneron, outside the submitted work. PA has served as a consultant for Merck, BMS, Pfizer, Affimed, Adaptive, Infinity, ADC Therapeutics, Celgene, Morphosys, Daiichi Sankyo, Miltenyi, Tessa, GenMab, C4, and Enterome; received research funding from Merck, BMS, Affimed, Adaptive, Roche, Tensha, Otsuka, Sigma Tau, Genentech, IGM and received honoraria from Merck and BMS, outside the submitted work. RJS has served as a consultant for Gilead, Rheos Therapeutics, Jazz, Cugene, Mana Therapeutics, VOR, and Novartis; served on data safety monitoring committees for Juno; served on board of directors for Kiadis and Be the Match/ NMDP, outside the submitted work. HTK has served as a consultant for Miltenyi, outside the submitted work. The remaining authors declare no competing financial interests.

Contributions: HTK conceived and designed the study, performed statistical analysis, interpreted the data and wrote the manuscript; JRB, CJW and MD conceived the study; POB and JRB compiled the outcome data, provided FISH data and annotated the cytogenetic data; JRB and JR edited the manuscript. All authors contributed to the manuscript review and approved the final version for submission.

Acknowledgments: we thank the patients and their families, the research coordinators, research nurses, and advanced practice providers.

Funding: this work was supported by research funding from the National Cancer Institute (P01CA229092) and the Ted and Eileen Pasquarello Tissue Bank in Hematologic Malignancies.

References

1. Wang Y, Tschautscher MA, Rabe KG, et al. Clinical characteristics and outcomes of Richter transformation: experience of 204 patients from a single center. Haematologica. 2020;105(3):765-773.
2. Rossi D, Spina V, Gaidano G. Biology and treatment of Richter syndrome. Blood. 2018;131(25):2761-2772.
3. Allan JN, Furman RR. Current trends in the management of Richter's syndrome. Int J Hematol Oncol. 2019;7(4):IJH09.
4. Kadri S, Lee J, Fitzpatrick C, et al.Clonal evolution underlying leukemia progression and Richter transformation in patients with ibrutinib-relapsed CLL. Blood Adv. 2017;1(12):715-727.
5. Maddocks KJ, Ruppert AS, Lozanski G, et al. Etiology of ibrutinib therapy discontinuation and outcomes in patients with chronic lymphocytic leukemia. JAMA Oncol. 2015;1(1):80-87.
6. Jain P, Thompson PA, Keating M, et al. Long-term outcomes for patients with chronic lymphocytic leukemia who discontinue ibrutinib. Cancer. 2017;123(12):2268-2273.
7. Dreger P, Schnaiter A, Zenz T, et al. TP53, SF3B1, and NOTCH1 mutations and outcome of allotransplantation for chronic lymphocytic leukemia: six-year follow-up of the GCLLSG CLL3X trial. Blood. 2013;121(16):3284-3288.
8. Dreger P, Montserrat E. European Society for Blood and Marrow Transplantation (EBMT); European Research Initiative on CLL (ERIC). Where does allogeneic stem cell transplantation fit in the treatment of chronic lymphocytic leukemia? Curr Hematol Malig Rep. 2015;10(1):59-64.
9. Tsimberidou AM, O'Brien S, Khouri I, et al. Clinical outcomes and prognostic factors in patients with Richter's syndrome treated with chemotherapy or chemoimmunotherapy with or without stem-cell transplantation. J Clin Oncol. 2006;24(15):2343-2351.
10. Cwynarski K, Van Biezen A, De Wreede L, et al. Autologous and allogeneic stem-cell transplantation for transformed chroniclymphocytic leukemia (Richter's syndrome): a retrospective analysis from the chronic lymphocytic leukemia subcommittee of the chronicleukemia working party and lymphoma working party of the European Group for Blood and Marrow Transplantation. J Clin Oncol. 2012;30(18):2211-2217.
11. Kharfan-Dabaja MA, Kumar A, Stingo F, et al. Allogeneic hematopoietic cell transplantation for richter syndrome: a single-centerexperience.Clin. Lymphoma. Myeloma Leuk. 2018:18(1):e35-e39.
12. Kim HT, Ahn KW, Hu ZH, et al Prognostic score and cytogenetic risk classification for reduced intensity conditioning allogeneic HCT in CLL patients: CIBMTR report. Clin Cancer Res. 2019;25(16):5143-5155.
13. Kim HT, Shaughnessy CJ, Rai SC, et al. Outcome of high-risk chronic lymphocytic leukemia patients undergoing allogeneic hematopoietic cell transplant after prior targeted therapy. Blood Adv. 2020; 4(17):4113-4123.
14. Fenske T, Ahn K, Graff T, et al. Allogeneic transplantation provides durable remission in a subset of DLBCL patients relapsing after autologous transplantation. Br J Haematol. 2016;174(2):235-248.
15. Kittai AS, Bond DA, William B, et al. Clinical activity of axicabtagene ciloleucel in adult patients with Richter syndrome. Blood Adv. 2020; 4(19):4648-4652.
16. Rossi D, Spina V, Deambrogi C, et al. The genetics of Richter syndrome reveals disease heterogeneity and predicts survival after transformation. Blood. 2011;117(12):3391-3401.