Emerging Clinical Activity of REGN1979, an Anti-CD20 x Anti-CD3 Bispecific Antibody, in Patients With Relapsed/Refractory B-Cell Non-Hodgkin Lymphoma (Follicular Lymphoma, Diffuse Large B-Cell Lymphoma, and Other B-Cell Non-Hodgkin Lymphoma Subtypes)

Rajat Bannerji[1], Jon Arnason[2], Ranjana Advani[3], Jennifer R. Brown[4], John Allan[5], Stephen Ansell[6], Jeffrey Barnes[7], Susan O'Brien[8], Julio Chavez[9], Johannes Düll[10], Andreas Rosenwald[11], Robert Charnas[12], Srikanth R. Ambati[12], Lieve Adriaens[13], Melanie Ufkin[12], Xiaoyu Yan[12], Jingjin Li[13], Mark Navarro[12], Peter Gasparini[12], Vladimir Jankovic[12], Nathalie Fiaschi[12], Wen Zhang[12], Sara Hamon[12], Gavin Thurston[12], Andrew J Murphy[12], George D Yancopoulos[12], Israel Lowy[12], David Sternberg[12], Max S. Topp[10]

[1]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA; [2]Beth Israel Deaconess Medical Center, Boston, MA, USA; [3]Stanford University, Stanford, CA, USA; [4]Dana-Farber Cancer Institute, Boston, MA, USA; [5]Weill Cornell Medicine, New York, NY, USA; [6]Mayo Clinic, Rochester, MN, USA; [7]Massachusetts General Hospital, Boston, MA, USA; [8]University of California, Irvine, Orange, CA, USA; [9]Moffitt Cancer Center, Tampa, FL, USA; [10]University Hospital of Würzburg, Würzburg, Germany; [11]University of Würzburg, Würzburg, Germany; [12]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; [13]Regeneron Pharmaceuticals, Inc., Basking Ridge, NJ, USA.

Introduction

- Despite high response rates with the initial therapy of advanced B-cell non-Hodgkin lymphoma (B-NHL), disease relapse is common, particularly in patients with clinical or molecular features associated with poor prognosis.[1,2]
- The CD20 antigen is a validated target for immunotherapy in patients with B-NHL; for example, the anti-CD20 monoclonal antibody (mAb) rituximab administered as induction and maintenance monotherapy in patients with previously untreated, Stage II or higher, asymptomatic non-bulky follicular lymphoma (FL) is associated with an overall response rate (ORR) of 88% and a complete response (CR) rate of 51% at 7 months.[3] However, response rates are much lower in relapsed/refractory B-NHL and in patients with bulky disease.[4]
- REGN1979 is a bispecific, human, anti-CD20 × anti-CD3 mAb based on an IgG4 isotype.[5]
- REGN1979 is designed to cross-link CD3-expressing T-cells and CD20+ B-cells, directing the T-cells to the tumor cells to enhance tumor killing independent of T-cell receptor recognition.[5,6]
- The hypothesis is that REGN1979 will result in improved rates and durability of response in patients with heavily pre-treated relapsed/refractory B-NHL.
- REGN1979 is being studied in patients with relapsed/refractory B-NHL in two separate ongoing clinical trials: one as a monotherapy and the other in combination with the anti-PD-1 antibody cemiplimab. This poster is an update on REGN1979 administered as a single agent.

Objectives

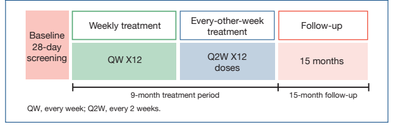
- Primary objective is to assess safety, tolerablity, and dose-limiting toxicities (DLTs) of REGN1979.
- Secondary objectives are to:
  - Characterize the pharmacokinetic profile;
  - Assess immunogenicity of REGN1979, as measured by anti-REGN1979 antibodies;
  - Study antitumor activity.

Methods

Study design

- Ongoing Phase 1, open label, multicenter study of REGN1979 monotherapy in patients with relapsed/refractory B-NHL and chronic lymphocytic leukemia, who were previously treated with CD20-directed therapy.
- Study consisted of a dose-escalation phase and an expansion phase.
- Key inclusion criteria:
  - Age ≥18 years;
  - Active CD20+ B-cell malignancy not responsive to prior therapy and for whom treatment with an anti-CD20 antibody is appropriate;
  - Prior treatment with an anti-CD20 antibody;
  - At least one bi-dimensionally measurable lesion;
  - Adequate bone marrow and organ function.
- Traditional 3 + 3 dose-escalation design with allowance of expansion.
- Each dose level cohort receives an initial starting dose of REGN1979 followed by a higher step-up dose. At the 12 mg dose cohort, an intermediate dose is introduced.

Figure 1. Study drug dosing



QW, every week; Q2W, every 2 weeks.

Results

Patient disposition, treatment exposure, baseline characteristics, and prior treatment history

- As of September 18, 2018, 68 patients with B-NHL were treated with REGN1979 monotherapy.
- Patients receiving doses up to 40 mg and 80 mg of REGN1979 were included in the efficacy and safety analyses, respectively.

Table 1. Patient disposition

n (%)	N=68
Remained on treatment	13 (19.1)
Completed treatment	14 (20.6)
Discontinued	41 (60.3)
Progressive disease (PD)	27 (39.7)
Patient decision	4 (5.9)
Death	3 (4.4)
Other*	3 (4.4)
Adverse events	2 (2.9)
Physician decision	2 (2.9)

*One patient had sub-optimal response and was retreated at a higher dose of REGN1979, one patient received other therapy, and one patient transitioned to palliative measures only.

Table 2. Number of doses; duration of exposure and follow-up

Median number of doses (range)	8 (1–24)
Median duration of exposure, weeks (range)	10.5 (0.1–39.0)
Median duration of follow-up, weeks (range)	12.4 (0.1–63.4)

Table 3. Baseline characteristics and prior treatment history

	REGN1979 dose groups		
	<5 mg (n=27)	≥5 mg (n=41)	Total (N=68)
Median age, years (range)	66 (30–85)	69 (36–82)	66 (30–85)
Male, n (%)	23 (85.2)	28 (68.3)	51 (75.0)
ECOG Performance Status, n (%)			
0	12 (44.4)	18 (43.9)	30 (44.1)
1	15 (55.6)	23 (56.1)	38 (55.9)
Ann Arbor stage at study entry, n (%)			
I–II	7 (25.9)	6 (14.6)	13 (19.1)
III–IV	20 (74.1)	35 (85.4)	55 (80.9)
NHL diagnosis, n (%)			
DLBCL	15 (55.6)	22 (53.7)	37 (54.4)
FL (any grade)	8 (29.6)	12 (29.3)	20 (29.4)
MCL	3 (11.1)	2 (4.9)	5 (7.4)
MZL	1 (3.7)	4 (9.8)	5 (7.4)
WM	0	1 (2.4)	1 (1.5)
Median prior lines of systemic therapy, n (range)	3 (1–6)	3 (1–11)	3 (1–11)
Refractory/relapsed to the last-line of systemic therapy*, n (%)			
Refractory†	26 (96.3)	28 (68.3)	54 (79.4)
Relapsed‡	1 (3.7)	12 (29.3)	13 (19.1)
Refractory/relapsed to most recent anti-CD20 antibody therapy, n (%)			
Refractory†	24 (88.9)	26 (63.4)	50 (73.5)
Relapsed‡	3 (11.1)	15 (36.6)	18 (26.5)
Refractory/relapsed to anti-CD20 antibody therapy when used as the last-line of therapy, n (%)§			
Refractory†	18 (66.7)	20 (48.8)	38 (55.9)
Relapsed‡	0	10 (24.4)	10 (14.7)
Median time from end of last prior anti-CD20 antibody therapy to first dose of REGN1979, months (range)	3.3 (1–100)	7.5 (0–60)	7.1 (0–100)

Six patients (8.8%) had previous stem cell transplantations. *Relapse/refractory status of one patient is missing. †Relapse between 6 months or greater. ‡Total of 20 patients did not receive anti-CD20 antibody therapy as the last-line of therapy.

DLBCL, diffuse large cell B-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; WM, Waldenström macroglobulinemia.

Safety

- Majority of adverse events were mild to moderate in severity.
- No DLTs reported to date in patients with B-NHL.
- Fifty-one patients (75.0%) experienced at least one adverse event of grade 3/4/5 severity.
- No clinically significant neurotoxicity has been observed, including no seizure and/or encephalopathy.
- Twenty-eight patients (41.2%) experienced at least one nervous system adverse event of any grade and attribution; those occurring in two or more patients were headache (19.1%), dizziness (13.2%), paresthesia (4.4%), neuropathy peripheral (4.4%), and somnolence (2.9%).
  - Two patients experienced grade ≥3 nervous system events: one had depressed level of consciousness that was judged by the investigator to be unrelated to the study drug and the other patient had transient (<48 hours) somnolence in the setting of cytokine release syndrome (CRS) associated with study drug. No neurological event required termination of the study drug.
- Twenty-eight patients (41.2%) experienced at least one adverse event of infection and infestations, of which seven patients (10.3%) had at least one grade 3/4 event.
- Two patients discontinued treatment due to related adverse events: grade 3 hemolysis and grade 3 fatigue.
- Three patients died due to adverse events during the study. Reasons for death per investigator and sponsor assessments are as follows:
  - A fatal event of multi-organ failure deemed unrelated to REGN1979. Primary reason of death was due to PD;
  - A fatal event of cardiac arrest deemed unrelated to REGN1979;
  - A fatal event of gastric perforation attributed to REGN1979. The patient had demonstrated involvement of the gastric wall with lymphoma.

Table 4. Summary of adverse events

Events of any grade*, n (%)	N=68
Any	66 (97.1)
Serious	38 (55.9)
Led to discontinuation	2 (2.9)
Most common adverse events (≥20%)	
Pyrexia	51 (75.0)
Chills	33 (48.5)
CRS	32 (47.1)
Fatigue	24 (35.3)
Increased C-reactive protein	21 (30.9)
Anemia	17 (25.0)
Hypotension	17 (25.0)
Infusion-related reaction	17 (25.0)
Nausea	17 (25.0)
Thrombocytopenia	16 (23.5)
Neutropenia	15 (22.1)
Hypophosphatemia	14 (20.6)
Edema peripheral	14 (20.6)
Grade 3/4 events*, n (%)	**N=68**
Most common adverse events (≥3 patients)	
Neutropenia	12 (17.6)
Lymphopenia	12 (17.6)
Anemia	9 (13.2)
Thrombocytopenia	7 (10.3)
Hypophosphatemia	6 (8.8)
Leukopenia	4 (5.9)
CRS	4 (5.9)
Fatigue	4 (5.9)
Hypotension	4 (5.9)
Increased aspartate aminotransferase	4 (5.9)

*Adverse events graded using National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03, except for CRS graded according to Lee et al 2014.[7]

Efficacy

- The data cut-off date for the analysis of clinical efficacy was November 16, 2018 and includes patients who were treated with REGN1979 ≤40 mg as of data cut-off (September 18, 2018).
- Tumor responses were assessed based on computed tomography (CT) measurements according to the International Working Group (Cheson 2007) criteria and based on metabolic assessment using fludeoxyglucose-positron emission tomography (FDG-PET) per the Lugano criteria.[8,9]

Pharmacodynamics

Serum cytokine levels and infusion-related reactions (IRR)/CRS events

- Elevated levels of serum cytokines (IL-6, IL-10, and TNF-α) were observed with REGN1979 dosing (**Figure 3A**).
- Serum cytokine levels decreased over time; no apparent dose-dependent trend was observed between REGN1979 ≥5 mg and <5 mg dose groups (**Figure 3A**).
- Higher peak serum cytokine levels corresponded to increased severity of IRR/CRS events (data not shown).
- Incidence and severity of IRR/CRS events decreased over time with current administration procedures (**Figure 3B**).
- No correlation between higher peak serum cytokine levels and clinical efficacy was observed (data not shown).

Table 5. Best overall response according to Cheson 2007 criteria in patients with relapsed/refractory FL grade 1–3a*

	REGN1979 dose groups		
	<5 mg (n=7)	≥5–≤12 mg (n=5)	≥18–≤40 mg (n=5)
ORR, n (%)	1 (14.3)	5 (100.0)	5 (100.0)
CR, n (%)	1 (14.3)	4 (80.0)	4 (80.0)
PR, n (%)	0	1 (20.0)	1 (20.0)
Responding patients who did not progress during study treatment, n/N (% of responders)	1 (100.0)	4 (80.0)	5 (100.0)

*Median number of prior systemic therapies, n (range): 4 (1–11).

Table 6. Best overall response according to Cheson 2007 criteria in patients with relapsed/refractory DLBCL*

	REGN1979 dose groups		
	<5 mg (n=15)	≥5–≤12 mg (n=11)	≥18–≤40 mg (n=10)
ORR, n (%)	3 (20.0)	2 (18.2)	6 (60.0)
CR, n (%)	0	1 (9.1)	2 (20.0)
PR, n (%)	3 (20.0)	1 (9.1)	4 (40.0)
Responding patients who did not progress during study treatment, n/N (% of responders)	1 (33.3)	1 (50.0)	3 (50.0)

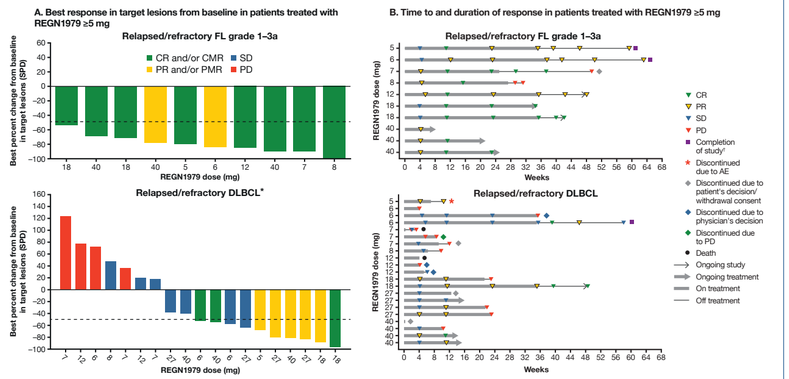
*Median number of prior systemic therapies, n (range): 3 (1–7).

Table 7. Best overall response according to Cheson 2007 criteria in patients with B-NHLs-other*,†

	REGN1979 dose groups		
	<5 mg (n=5)	≥5–≤12 mg (n=3)	≥18–≤40 mg (n=4)
ORR, n (%)	2 (40.0)	1 (33.3)	3 (75.0)
CR, n (%)	0	0	2 (50.0)
PR, n (%)	2 (40.0)	1 (33.3)	1 (25.0)
Responding patients who did not progress during study treatment, n/N (% of responders)	0	1 (100.0)	2 (66.7)

*Median number of prior therapies, n (range): 3 (1–5); †Includes patients with MCL, MZL, WM, FL grade unknown, and FL grade 3b.

Figure 2. Tumor response in patients with relapsed/refractory FL grade 1–3a and DLBCL

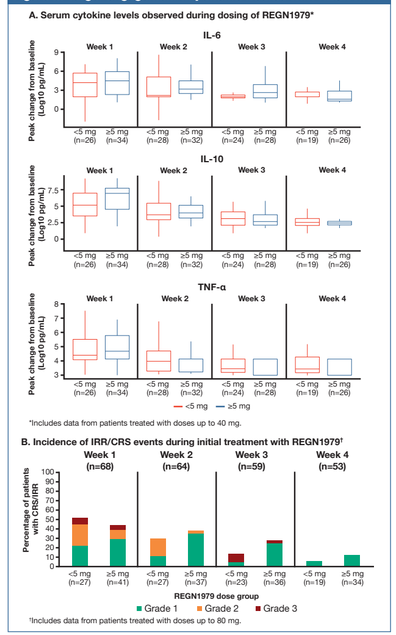


*Two patients discontinued prior to the first on-treatment disease assessment; †Patients completed the study before implementing a protocol amendment that allows a 15-month follow-up.
CMR, complete metabolic response; PMR, partial metabolic response; PR, partial response; SD, stable disease; SPD, sum of the products of the diameters.

Lymph node tissue biomarkers

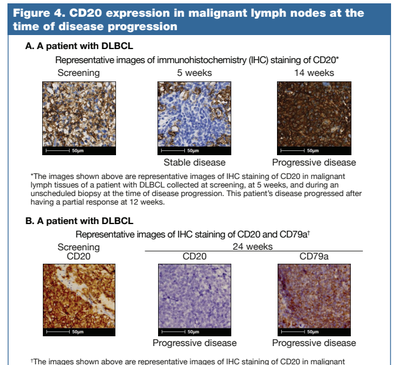
- Clinical response to REGN1979:
  - Was associated with a decrease in area stained for B-cells and a trend towards increased area stained for T-cells (data not shown);
  - Was achieved in patients with both high and low levels of CD20 expression (% stained area) in tissues at baseline (data not shown).
- Relapse following a clinical response was associated with either maintenance of CD20 expression or CD20 loss, suggesting antigen-dependent and antigen-independent disease escape mechanisms (**Figure 4**).

Figure 3. Target engagement in patients treated with REGN1979



*Includes data from patients treated with doses up to 40 mg.
†Includes data from patients treated with doses up to 80 mg.

Figure 4. CD20 expression in malignant lymph nodes at the time of disease progression



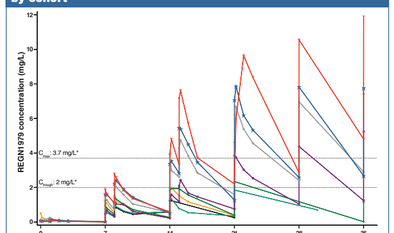
*The images shown above are representative images of IHC staining of CD20 in malignant lymph tissues of a patient with DLBCL collected at screening, at 5 weeks, and during an unscheduled biopsy at the time of disease progression. This patient's disease progressed after having a partial response at 12 weeks.

†The images shown above are representative images of IHC staining of CD20 in malignant lymph node tissues of a patient with DLBLC collected at screening and from a biopsy at the time of disease progression. Corresponding staining of CD79a at disease progression was performed to confirm the CD20-negative B-cell lymphoma phenotype. This patient's disease progressed after having a partial response at 12 weeks.

Pharmacokinetics

- Serum concentrations of REGN1979 generally increased in a nearly dose-proportional manner (**Figure 5**).
- The exposure at 40 mg in patients with B-NHL was in a range similar to the concentration range that resulted in tumor killing in established B-cell (Raji) tumor-bearing NOD-Scid IL2rγ^{null} mouse model.

Figure 5. Mean (±SD) concentrations of REGN1979 versus time by cohort



*The horizonal lines of C_{max} and C_{trough} represent effective concentrations in mice at which the growth of established B-cell (Raji) tumors was inhibited.

Conclusions

- In the dose-escalation part of this Phase 1 study, REGN1979, an anti-CD20 x anti-CD3 bi-specific antibody, was well tolerated in patients with relapsed/refractory B-NHL. There have been no DLTs reported to date in patients with B-NHL.
  - CRS and IRR, which are adverse events associated with bispecific antibody or CAR T therapy, were observed with REGN1979 therapy, but did not require treatment discontinuation.
  - No clinically significant neurotoxicity was observed to date with REGN1979, including no seizures and/or encephalopathy.
- Treatment with REGN1979 ≥5 mg has shown marked clinical efficacy in heavily pretreated patients with relapsed/refractory FL grade 1–3a (ORR: 100% [8/10 CR; 2/10 PR]). These data warrant further clinical investigation in relapsed/refractory FL and in previously untreated FL, either as a single agent or in combination therapy.
- Data indicate improved efficacy with higher doses of REGN1979 (i.e. 18–40 mg) compared with the lower doses in heavily pretreated relapsed/refractory DLBCL (ORR <5 mg: 20%; 5–12 mg: 18%; 18–40 mg: 60%] and in other B-NHL subtypes (ORR <5 mg: 40%; 5–12 mg: 33%; 18–40 mg: 75%). Dose escalation is continuing.

References

1. Chao MP. *Cancer Manag Res.* 2013;5:251–269.
2. Swerdlow SH et al. *Blood.* 2016;127:2375–2390.
3. Ardeshna KM et al. *Lancet Oncol.* 2014;15:424–435.
4. Ghielmini M et al. *Blood.* 2004;103:4416–4423.
5. Smith EJ et al. *Sci Rep.* 2015;5:17943.
6. Choi BD et al. *Expert Opin Biol Ther.* 2011;11:843–853.
7. Lee DW et al. *Blood.* 2014;124:188–195.
8. Cheson BD. *Hematol Oncol Clin North Am.* 2007;21:841–854.
9. Cheson BD et al. *J Clin Oncol.* 2014;32:3059–3068.

Conflict of interest disclosure

Rajat Bannerji has received consultancy fees from AbbVie, Inc., Celgene, and Regeneron Pharmaceuticals, Inc. **Jon Arnason** has received consultancy fees from Regeneron Pharmaceuticals, Inc. **Ranjana Advani** has received advisory/consultancy fees from Bayer Healthcare Pharmaceuticals, LLC, Cell Medica, Ltd, AstraZeneca, Autolus, Ltd, Gilead Sciences, Inc./Kite Pharma, Inc., Takeda Pharmaceuticals, Ltd, and Kyowa Kirin Pharmaceutical Developments, Inc.; advisory/consultancy fees and institutional research support from Bristol Myers Squibb, Pharmacyclics, LLC, Seattle Genetics, and Roche/Genentech; institutional research support from Regeneron Pharmaceuticals, Inc., Infinity Pharmaceuticals, Millenium Pharmaceuticals, Janssen Pharmaceuticals, Inc., Kura Oncology, Inc., Merck & Co, Agensys, Inc., Celgene, and Forty Seven, Inc. **Jennifer R. Brown** has received honoraria from TG therapeutics, Inc., AbbVie, Inc., Acerta Pharma, AstraZeneca, BeiGene, Celgene, Genentech, Janssen Pharmaceuticals, Inc., Loxo Oncology, Inc., Novartis, Pfizer, Inc., Pharmacyclics, and Sunesis Pharmaceuticals; consultancy and research funding from Gilead and Verastem Oncology, Inc.; honoraria and research funding from Sun Pharmaceutics Industries, Ltd. **John Allan** received consultancy fees from Acerta Pharma; is a member of Board of Directors/advisory committees of Genentech; AbbVie, Inc., Verastem Oncology, Inc., and Sunesis Pharmaceuticals. **Stephen Ansell** has received research funding from Affimed, Bristol Myers Squibb, Celldex Therapeutics, Inc., LAM Therapeutics, Merck & Co, Seattle Genetics, Takeda Pharmaceuticals, Ltd, Regeneron Pharmaceutical, Inc., Trillium Therapeutics, Inc. and Pfizer, Inc. **Jeffrey Barnes** declares no conflict of interest. **Susan O'Brien** has received, consultancy fees from Amgen, Astellas Pharma, Celgene, GlaxoSmithKline, Aptose Biosciences, Inc., Janssen Pharmaceuticals, Inc., Janssen Group LLC, Alexion Pharmaceuticals, Inc.; consultancy and honoraria form AbbVie, Inc. and Janssen Pharmaceuticals, Inc.; consultancy and research funding from TG Therapeutics, Inc., Pfizer, Inc., Sunesis Pharmaceuticals, and Gilead. **Julio Chavez** is a member of Speakers Bureau of Janssen Pharmaceuticals, Inc., Board of Directors and Speakers Bureau of Genetech, and a member of Board of Directors or advisory committees at Kite Pharmaceuticals, Inc. and Novartis. **Johannes Düll** declares no conflict of interest. **Robert Charnas, Srikanth R. Ambati, Lieve Adriaens, Melanie Ufkin, Xiaoyu Yan, Jingjin Li, Mark Navarro, Peter Gasparini, Vladimir Jankovic, Nathalie Fiaschi, Wen Zhang, Sara Hamon, Gavin Thurston, Andrew J Murphy, George D Yancopoulos, Israel Lowy, and David Stemberg** are employees and shareholders of Regeneron Pharmaceuticals, Inc. **Mark Navarro** is an employee of Regeneron Pharmaceuticals, Inc. **Max S. Topp** is a member of advisory committees and has received research funding from Amgen, Boehringer Ingelheim, Regeneron Pharmaceuticals, Inc. and Roche.

Acknowledgments

The authors would like to thank the patients, their families, and all investigational site support staff involved in this study. Medical writing support under the direction of the authors was provided by Leleesha Samarawera, PhD, of Prime (Knutsford, UK) and funded by Regeneron Pharmaceuticals, Inc.

Poster presented at the 2018 American Society of Hematology, December 1–4, San Diego, CA.