SEQUOIA 5-Year Follow-Up in Arm C: Frontline Zanubrutinib Monotherapy in Patients With del(17p) and Treatment-Naive Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

CLL-745

Constantine S. Tam,[1] Paolo Ghia,[2,3] Mazyar Shadman,[4,5] Talha Munir,[6] Stephen S. Opat,[7] Patricia A. Walker,[8] Masa Lasica,[9] Ian W. Flinn,[10] Tian Tian,[11] Stephanie Agresti,[11] Jamie Hirata,[11] Jennifer R. Brown[12]

[1]Alfred Hospital and Monash University, Melbourne, VIC, Australia; [2]Università Vita-Salute San Raffaele, Milano, Italy; [3]Comprehensive Cancer Center, IRCCS Ospedale San Raffaele, Milano, Italy; [4]Fred Hutchinson Cancer Center, Seattle, WA, USA; [5]University of Washington, Seattle, WA, USA; [6]Leeds Teaching Hospitals NHS Trust, Leeds, UK; [7]Lymphoma Research Group, School of Clinical Sciences at Monash Health, Monash University, Clayton, VIC, Australia; [8]Peninsula Health and Peninsula Private Hospital, Melbourne, VIC, Australia; [9]St Vincent's Hospital Melbourne, Melbourne, VIC, Australia; [10]Tennessee Oncology/OneOncology, Nashville, TN, USA; [11]BeOne Medicines Ltd, San Carlos, CA, USA; [12]Dana-Farber Cancer Institute, Boston, MA, USA

CONCLUSIONS

- SEQUOIA Arm C reports on the largest prospective cohort of uniformly treated patients with del(17p) TN CLL/SLL
- With a median follow-up of 5-years, zanubrutinib demonstrates durable efficacy in patients with del(17p)
  - The estimated 60-month PFS with zanubrutinib was 72.2%, similar to that observed in patients without del(17p)[6]
  - PFS benefit was the same regardless of IGHV status
  - These results highlight that zanubrutinib overcomes the negative prognostic impact of high risk features of del(17p) and unmutated IGHV
- The benefit of zanubrutinib in patients with del(17p) was also demonstrated in the phase 3 ALPINE study, which demonstrated PFS superiority of zanubrutinib over ibrutinib[4]
- Long-term follow-up from SEQUOIA confirms the impressive zanubrutinib efficacy and good tolerability in patients with TN CLL/SLL with or without del(17p)

INTRODUCTION

- Zanubrutinib is a highly potent and selective next-generation Bruton tyrosine kinase (BTK) inhibitor that was designed to provide complete and sustained target inhibition and is the only BTK inhibitor to demonstrate superiority over ibrutinib in a head-to-head phase 3 trial[1-4]
- SEQUOIA (NCT03336333) is a registrational phase 3, open-label, randomized study that evaluated zanubrutinib in a broad range of patients with treatment-naive (TN) chronic lymphocytic leukemia (CLL), including those with high-risk features[5-7]
  - In Arms A and B, zanubrutinib monotherapy (Arm A) demonstrated superior progression-free survival (PFS) compared with bendamustine + rituximab (Arm B) in patients without del(17p) at 26.2-month follow-up and sustained PFS benefit at 5-year follow-up (Arm A: 75.8%)[5,6]
  - In Arm C, patients with del(17p) treated with zanubrutinib monotherapy have achieved high overall response rates and PFS, despite being at high risk for disease progression and death[7]
- Here, we present updated results from SEQUOIA Arm C after approximately 5 years of follow-up in a historically difficult to treat del(17p) patient population
  - To our knowledge, this reports the largest cohort of uniformly treated patients with del(17p) TN CLL/small lymphocytic lymphoma (SLL)

METHODS

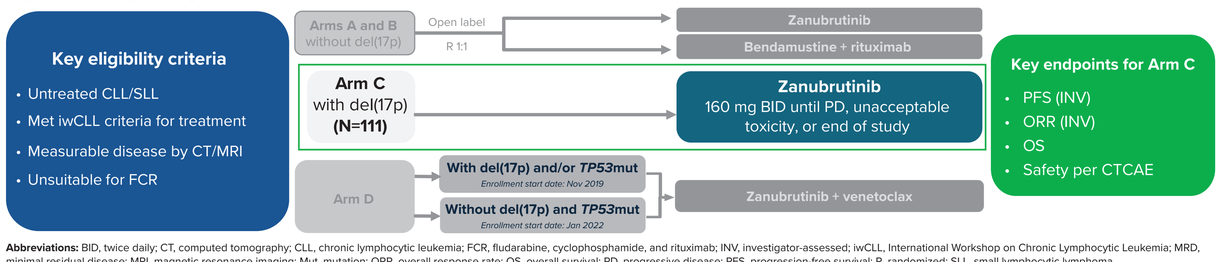
Study Design

- Arm C is a nonrandomized cohort of SEQUOIA patients with del(17p) that received zanubrutinib monotherapy; key study endpoints are shown in **Figure 1**
- Overall response rate (ORR) was assessed by investigator per the 2008 International Workshop on Chronic Lymphocytic Leukemia (iwCLL) guidelines[8] with modification for treatment-related lymphocytosis[9] for patients with CLL and per Lugano criteria[10] for patients with SLL
- ORR was defined as achievement of partial response with lymphocytosis (PR-L) or better

Assessments

- Sensitivity analyses were performed for PFS and overall survival with deaths due to COVID-19 infection, censored at the time of death if no prior progression was observed
- Response assessments were performed every 12 weeks after the first dose of study drug for 96 weeks, then every 24 weeks until progressive disease
- Adverse events (AEs) were graded by NCI-CTCAE version 4.03 and documented from the time of first dose of study drug, until 30 days after the last dose of study drug, or until disease progression (whichever occurred later) or until the first day of a new CLL/SLL treatment

Figure 1. Study Design



Abbreviations: BID, twice daily; CT, computed tomography; CLL, chronic lymphocytic leukemia; FCR, fludarabine, cyclophosphamide, and rituximab; INV, investigator-assessed; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MRD, minimal residual disease; MRI, magnetic resonance imaging; Mut, mutation; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; R, randomized; SLL, small lymphocytic lymphoma.

RESULTS

Disposition and Baseline Characteristics

- Between Feb 2018 and Mar 2019, 111 treatment-naive patients with del(17p) were enrolled to receive zanubrutinib
- As of April 30, 2024, at a median follow-up of 65.8 months (range, 5.0-75.0), 69 patients (62.2%) remained on treatment; the most common causes for treatment discontinuation were AEs (17.1%) and progressive disease (15.3%)
- Baseline demographic and disease characteristics are shown in **Table 1**

Table 1. Baseline Demographics and Clinical Characteristics

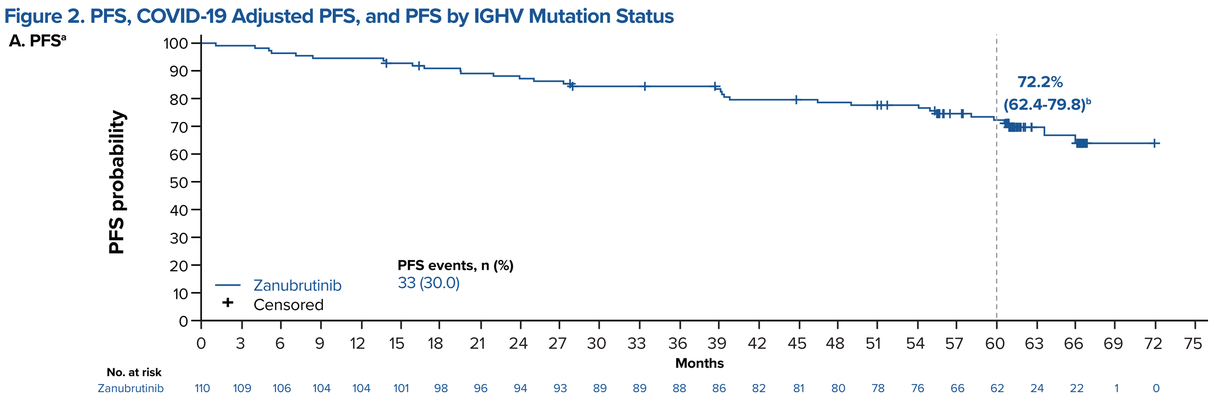
	All patients (N=111)
Age, median (range), years	71 (42-87)
≥65 years, n (%)	95 (85.6)
Male, n (%)	79 (71.2)
ECOG PS 0-1, n (%)	97 (87.3)
CLL, n (%)	100 (90.1)
SLL, n (%)	11 (9.9)
Binet stage C, n (%)[a]	37 (37.0)
Bulky disease, n (%)	
LDi ≥5 cm	44 (39.6)
LDi ≥10 cm	12 (10.8)
Median time from initial diagnosis, months	21.39
***TP53* mutated, n (%)**	47 (42.3)
del(17p), n (%)	110 (99.1)
del(17)p and *TP53* mutated, n (%)	47 (42.3)
IGHV mutated, n (%)	36 (32.4)
IGHV unmutated, n (%)	67 (60.4)
Complex karyotype, n (%)	
≥3 abnormalities	31 (27.9)
≥5 abnormalities	21 (18.9)

[a]Binet stage was assessed at study entry for patients with CLL.
Abbreviations: CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy-chain variable region; LDi, longest diameter; SLL, small lymphocytic lymphoma.

Efficacy

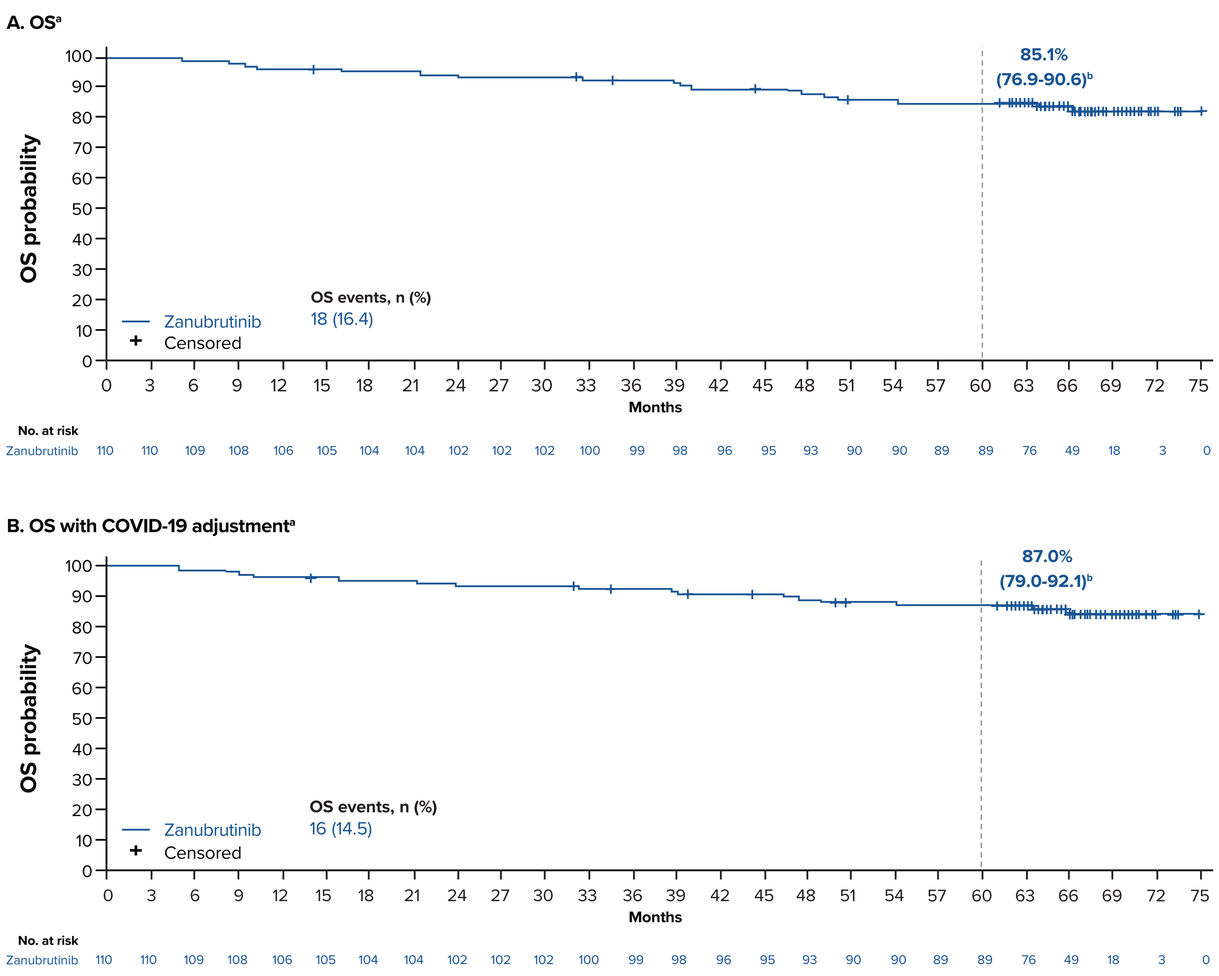
- Median PFS for zanubrutinib was not reached
- Estimated 60-month PFS rate (95% CI) was 72.2% (62.4-79.8) (**Figure 2A**)
  - When adjusted for COVID-19 impact, estimated 60-month PFS rate (95% CI) was 73.0% (63.3-80.6) (**Figure 2B**)
  - In patients with mutated and unmutated immunoglobulin heavy-chain variable region (IGHV), estimated 60-month PFS rate (95% CI) was 74.6% (56.9-85.9) and 70.7% (57.4-80.6), respectively (**Figure 2C**)
- In total, 18 deaths occurred in the study and median OS was not reached
- Estimated 60-month OS rate (95% CI) was 85.1% (76.9-90.6) (**Figure 3A**)
  - When adjusted for COVID-19 the estimated 60-month OS rate (95% CI) was 87.0% (79.0-92.1) (**Figure 3B**)

Figure 2. PFS, COVID-19 Adjusted PFS, and PFS by IGHV Mutation Status



[a]Data are presented in patients with del(17p), confirmed by central laboratory (N=110). [b]95% CI values.
Abbreviations: PFS, progression-free survival; IGHV, immunoglobulin heavy-chain variable region.

Figure 3. OS and COVID-19 Adjusted OS



[a]Data are presented in patients with del(17p), confirmed by central laboratory (N=110). [b]95% CI values.
Abbreviations: OS, overall survival.

Best Overall Response

- The ORR was 97.3%, and the combined complete response/complete response with incomplete hematologic recovery rate (CR/CRi) was 18.2% (**Table 2**)

Table 2. Best Overall Response Rate

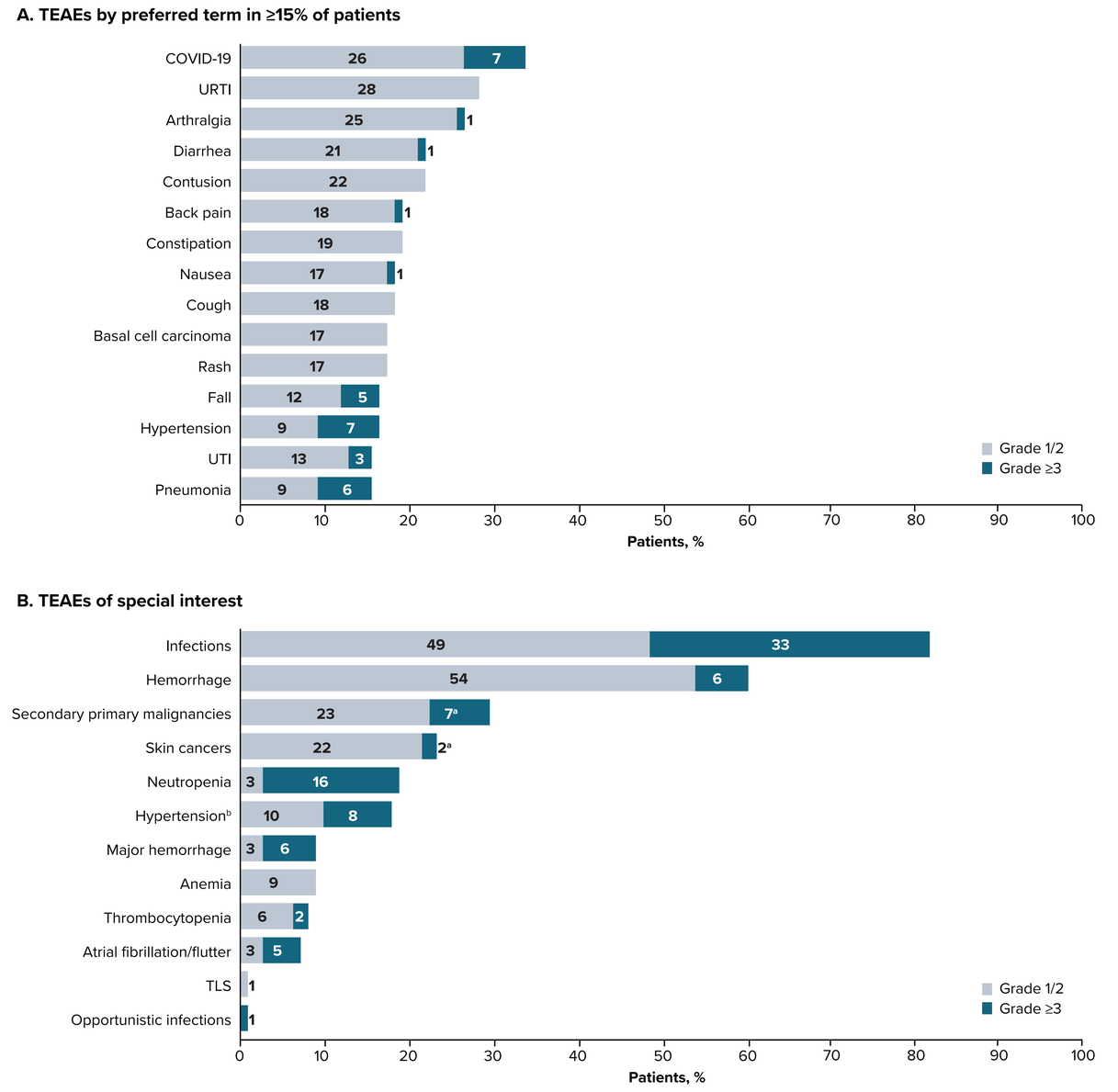
	Zanubrutinib (N=110)[a]
ORR, n (%)	107 (97.3)
Best overall response, n (%)	
CR/CRi	20 (18.2)
nPR	3 (2.7)
PR	84 (76.4)
PR-L	0
SD	2 (1.8)
PD	1 (0.9)

[a]Patients with del(17p), confirmed by central laboratory.
Abbreviations: CR, complete response; CRi, complete response with incomplete hematopoietic recovery; ORR, overall response rate; nPR, nodular partial response; PD, progressive disease; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease.

Safety

- The most common treatment-emergent adverse events (TEAEs) and TEAEs of special interest are presented in **Figure 4**
- AEs led to death in 6 patients (5.4%)

Figure 4. TEAEs and TEAEs of Special Interest



[a]Includes two patients with malignant melanoma. [b]Includes hypertension, increased blood pressure, hypertensive crisis and hypertensive heart disease.
Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event; TLS, tumor lysis syndrome; URTI, upper respiratory tract infection; UTI, urinary tract infection.

REFERENCES

1. Guo Y, et al. *J Med Chem*. 2019;62(17):7923-7940.
2. Brukinsa (zanubrutinib). Prescribing information. BeOne Medicines Ltd; 2024.
3. Brukinsa (zanubrutinib). Summary of product characteristics. BeOne Medicines Ltd; 2024.
4. Brown J, et al. *Blood*. 2024;144(26):2706-2717.
5. Tam CS, et al. *Lancet Oncol*. 2022;23(8):1031-1043.
6. Shadman M, et al. *J Clin Oncol*. 2025;43(7):780-787.
7. Tam CS, et al. *Haematologica*. 2021;106(9):2354-2363.
8. Hallek M, et al. *Blood*. 2008;111(12):5446-5456.
9. Cheson BD, et al. *J Clin Oncol*. 2012;30(23):2820-2822.
10. Cheson BD, et al. *J Clin Oncol*. 2014;32(27):3059-3967.

ACKNOWLEDGMENTS

The authors thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centers.
This study was sponsored by BeOne Medicines Ltd. Medical writing support was provided by Manoshi Nath, MSc, of Nucleus Global, an Inizio company, and supported by BeOne Medicines.

DISCLOSURES

CST: Honoraria: AbbVie, Janssen, BeOne Medicines Ltd, AstraZeneca. **PG:** Honoraria: AbbVie, AstraZeneca, BeOne Medicines Ltd, BMS, Janssen, Galapagos, Lilly/Loxo, MSD, Roche; Research funding: AbbVie, AstraZeneca, BMS, Janssen. **MS:** Consultant: AbbVie, Genentech, AstraZeneca, Genmab, Janssen, BeOne Medicines Ltd, BMS, MorphoSys/Incyte, Kite Pharma, Lilly, Fate Therapeutics, Nurix, Merck; Research funding: Mustang Bio, Genentech, AbbVie, BeOne Medicines Ltd, AstraZeneca, Genmab, Morphosys/Incyte, Vincerx; Stock: Koi Biotherapeutics; Employment: BMS (spouse). **TM:** Honoraria: BeOne Medicines Ltd, AstraZeneca, Sobi, Roche, Janssen, AbbVie, Lilly; Consultant: AbbVie, BeOne Medicines Ltd, Sobi, Alexion, Novartis, Janssen, AstraZeneca, Lilly, Roche; Research grants: Janssen, AbbVie; Travel, accommodations, or expenses: Alexion, BeOne Medicines Ltd, AbbVie, Janssen, AstraZeneca; Advisory board: AbbVie, BeOne Medicines Ltd, AstraZeneca, Janssen. **SSO:** Current employment: Monash Health; Consultancy (includes expert testimony): AbbVie, AstraZeneca, BeOne Medicines Ltd, Janssen, Novartis; Research funding: AbbVie, AstraZeneca, BeOne Medicines Ltd, Gilead, Janssen, Novartis, Pharmacyclics, Roche, Takeda; Honoraria: AbbVie, AstraZeneca, Gilead, Janssen, Merck, Roche, Takeda. **PAW:** No disclosure. **ML:** Honoraria: Janssen, AbbVie; Advisory board: Janssen, Sobi, AbbVie, Recordati. **IWF:** Employment: OneOncology; Research grants (all payments made to institution): AbbVie, AstraZeneca, BeOne Medicines Ltd, BMS, Celgene, City of Hope National Medical Center, Epizyme, Fate Therapeutics, Genentech, Gilead Sciences, IGM Biosciences InnoCare Pharma, Incyte, Janssen, Kite Pharma, Loxo, Marker Therapeutics, Merck, MorphoSys, Myeloid Therapeutics, Novartis, Nurix, Pfizer, Roche, Seattle Genetics, TG Therapeutics, Vincerx Pharma, 2seventy bio; Consultant fees (all payments made to physician): Abbvie, BeOne Medicines Ltd, Genentech, Genmab, KITE, Vincerx; Board of Directors or advisory committee: OneOncology, Vincerx Adv Committee. **TT:** Employment and may own stock: BeOne Medicines Ltd. **SA:** Employment, may own stock, travel, accommodations, or expenses: BeOne Medicines Ltd. **JH:** Employment: BeOne Medicines Ltd, Genentech; Stocks or other ownership: BeOne Medicines Ltd, Roche. **JRB:** Consultant: Abbvie, Acerta/AstraZeneca, Alloplex Biotherapeutics, BeOne Medicines Ltd, BMS, EcoR1, Galapagos NV, Genentech/Roche, Grifols Worldwide Operations, InnoCare Pharma Inc, Kite Pharma, Loxo/Lilly, Magnet Biomedicine, Merck, Pharmacyclics; Research funding: BeOne Medicines Ltd, Gilead, iOnctura, Loxo/Lilly, MEI Pharma, TG Therapeutics; Royalties: UpToDate; Data Safety Monitoring Board for Grifols Therapeutics.

CORRESPONDENCE: Mazyar Shadman, mshadman@fredhutch.org

Presented at the 2025 Society of Hematologic Oncology; September 3-6, 2025, Houston, TX
Data originally presented at the 2025 ASCO Annual Meeting; May 30-June 3, 2025; Chicago, IL, USA. Abstract 7011