Supplementary Appendix

Pirtobrutinib in Covalent BTK-Inhibitor Pre-treated Mantle Cell Lymphoma

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Supplementary Tables

Table S1. Overall response rate and duration of response in patients previously treated with ibrutinib, acalabrutinib, or zanubrutinib.

	Ibrutinib (n=59)	Acalabrutinib (n=31)	Zanubrutinib (n=6)
Overall response rate, % (95 CI)	59.3% (45.7-71.9)	58.1% (39.1-75.5)	50.0% (11.8, 88.2)
Best overall response, n (%)			
Complete response	13 (22.0)	5 (16.1)	1 (16.7)
Partial response	22 (37.3)	13 (41.9)	2 (33.3)
Stable disease	7 (11.9)	4 (12.9)	2 (33.3)
Progressive disease	11 (18.6)	4 (12.9)	1 (16.7)
Not evaluable[a]	6 (10.2)	5 (16.1)	0
Duration of response			
Patients with a response, n	35	18	3
Patients with censored data, n (%)	24 (68.6)	8 (44.4)	3 (100.0)
Median duration of response, mo (95% CI)	NR (7.46-NR)	6.93 (3.22-NR)	NR (NR-NR)
Median follow-up, mo	11.93	8.21	5.78

Overall response and best response were determined according to the 2014 Lugano criteria[20] and based on independent review committee assessment. [a]Patients without post-baseline disease assessment were not evaluable. NE, not estimable; mo, months

Table S2. Adverse events in at least 10% of the overall BRUIN safety population.

	Overall safety population (N=725)			
	Treatment-emergent AE, (≥10%), %		Treatment-related AE, %	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Adverse event				
Fatigue	191 (26.3)	12 (1.7)	64 (8.8)	6 (0.8)
Diarrhea	160 (22.1)	6 (0.8)	62 (8.6)	2 (0.3)
Contusion	138 (19.0)	0	91 (12.6)	0
Nausea	108 (14.9)	1 (0.1)	32 (4.4)	1 (0.1)
Cough	107 (14.8)	0	16 (2.2)	0
Anemia	101 (13.9)	56 (7.7)	34 (4.7)	13 (1.8)
Dyspnea	99 (13.7)	7 (1.0)	21 (2.9)	1 (0.1)
Arthralgia	94 (13.0)	3 (0.4)	23 (3.2)	0
Constipation	93 (12.8)	2 (0.3)	18 (2.5)	0
Back Pain	91 (12.6)	4 (0.6)	5 (0.7)	0
Neutrophil Count Decrease	89 (12.3)	77 (10.6)	51 (7.0)	43 (5.9)
Headache	88 (12.1)	2 (0.3)	29 (4.0)	1 (0.1)
Pyrexia	87 (12.0)	6 (0.8)	14 (1.9)	0
Oedema peripheral	83 (11.4)	1 (0.1)	6 (0.8)	0
Abdominal pain	80 (11.0)	6 (0.8)	11 (1.5)	1 (0.1)
Platelet count decreased	74 (10.2)	35 (4.8)	33 (4.6)	8 (1.1)
Neutropenia	73 (10.1)	62 (8.6)	47 (6.5)	37 (5.1)
Adverse event of special interest[a]				
Anemia	102 (14.1)	57 (7.9)	34 (4.7)	13 (1.8)
Neutropenia[b]	165 (22.8)	143 (19.7)	99 (13.7)	82 (11.3)
Thrombocytopenia	94 (13.0)	48 (6.6)	40 (5.5)	11 (1.5)
Infections	342 (47.2)	128 (17.6)	63 (8.7)	20 (2.8)
Bleeding Bruising[c] Hemorrhage	249 (34.3) 168 (23.2) 126 (17.4)	16 (2.2) 0 16 (2.2)	134 (18.5) 108 (14.9) 44 (6.1)	4 (0.6) 0 4 (0.6)
Bruising[c]	168 (23.2)	0	108 (14.9)	0
Hemorrhage	126 (17.4)	16 (2.2)	44 (6.1)	4 (0.6)
Atrial Fibrillation/Atrial Flutter[d]	19 (2.6)	7 (1.0)	5 (0.7)	1 (0.1)

Data are n (%).

There were 45 grade 5 adverse events, and 4 grade 5 adverse events considered treatment-related (1 COVID-19 pneumonia, 1 septic shock, 1 pneumonia necrotizing, and 1 respiratory failure).

[a]Adverse events of special interest are those that were previously associated with cBTK inhibitors and are all composite terms except hypertension.

[b]Combines neutrophil count decreased, neutropenia, febrile neutropenia, and neutropenic sepsis.

[c]Bruising includes contusion, petechia, ecchymosis, and increased tendency to bruise.

[d]Of 19 total afib/aflutter TEAEs, 6 occurred in patients with a prior medical history of atrial fibrillation.

Table S3. Treatment-emergent adverse events leading to treatment discontinuation.

Preferred Term	MCL safety population (n=164)	Overall safety population (N=725)
Any TEAE leading to treatment discontinuation	15 (9.1)	45 (6.2)
COVID-19 pneumonia	1 (0.6)	4 (0.6)
COVID-19	0	3 (0.4)
Myelodysplastic syndrome	1 (0.6)	3 (0.4)
Pneumonia	2 (1.2)	2 (0.3)
Sepsis	1 (0.6)	2 (0.3)
Squamous cell carcinoma	0	2 (0.3)
Abdominal pain	0	1 (0.1)
Acute kidney injury	1 (0.6)	1 (0.1)
Acute myeloid leukemia	0	1 (0.1)
Acute myocardial infarction	1 (0.6)	1 (0.1)
Alopecia	1 (0.6)	1 (0.1)
Anemia	0	1 (0.1)
Anal squamous cell carcinoma	1 (0.6)	1 (0.1)
Anxiety	0	1 (0.1)
Bacterial sepsis	0	1 (0.1)
Blood alkaline phosphatase increased	0	1 (0.1)
Cholecystitis	1 (0.6)	1 (0.1)
Chronic respiratory failure	0	1 (0.1)
Dyspnea	0	1 (0.1)
Eyelid ptosis	0	1 (0.1)
Fatigue	1 (0.6)	1 (0.1)
Febrile neutropenia	0	1 (0.1)
Gastrointestinal haemorrhage	0	1 (0.1)
Hyperkalaemia	0	1 (0.1)
Infective aneurysm	1 (0.6)	1 (0.1)
Mucormycosis	1 (0.6)	1 (0.1)
Multiple organ dysfunction syndrome	1 (0.6)	1 (0.1)
Myalgia	0	1 (0.1)
Neuropathy peripheral	0	1 (0.1)
Neutropenia	1 (0.6)	1 (0.1)
Neutrophil count decreased	1 (0.6)	1 (0.1)
Pancreatic duct rupture	0	1 (0.1)
Pancytopenia	0	1 (0.1)
Pneumonitis	1 (0.6)	1 (0.1)
Rash maculo-papular	0	1 (0.1)
Respiratory failure	0	1 (0.1)
Septic shock	0	1 (0.1)
Staphylococcal sepsis	0	1 (0.1)
Stent-graft endoleak	1 (0.6)	1 (0.1)
Streptococcal infection	1 (0.6)	1 (0.1)
Tumor pain	0	1 (0.1)
Urosepsis	0	1 (0.1)

Weight decreased	1 (0.6)	1 (0.1)

Table S4. Treatment-related adverse events leading to treatment discontinuation.

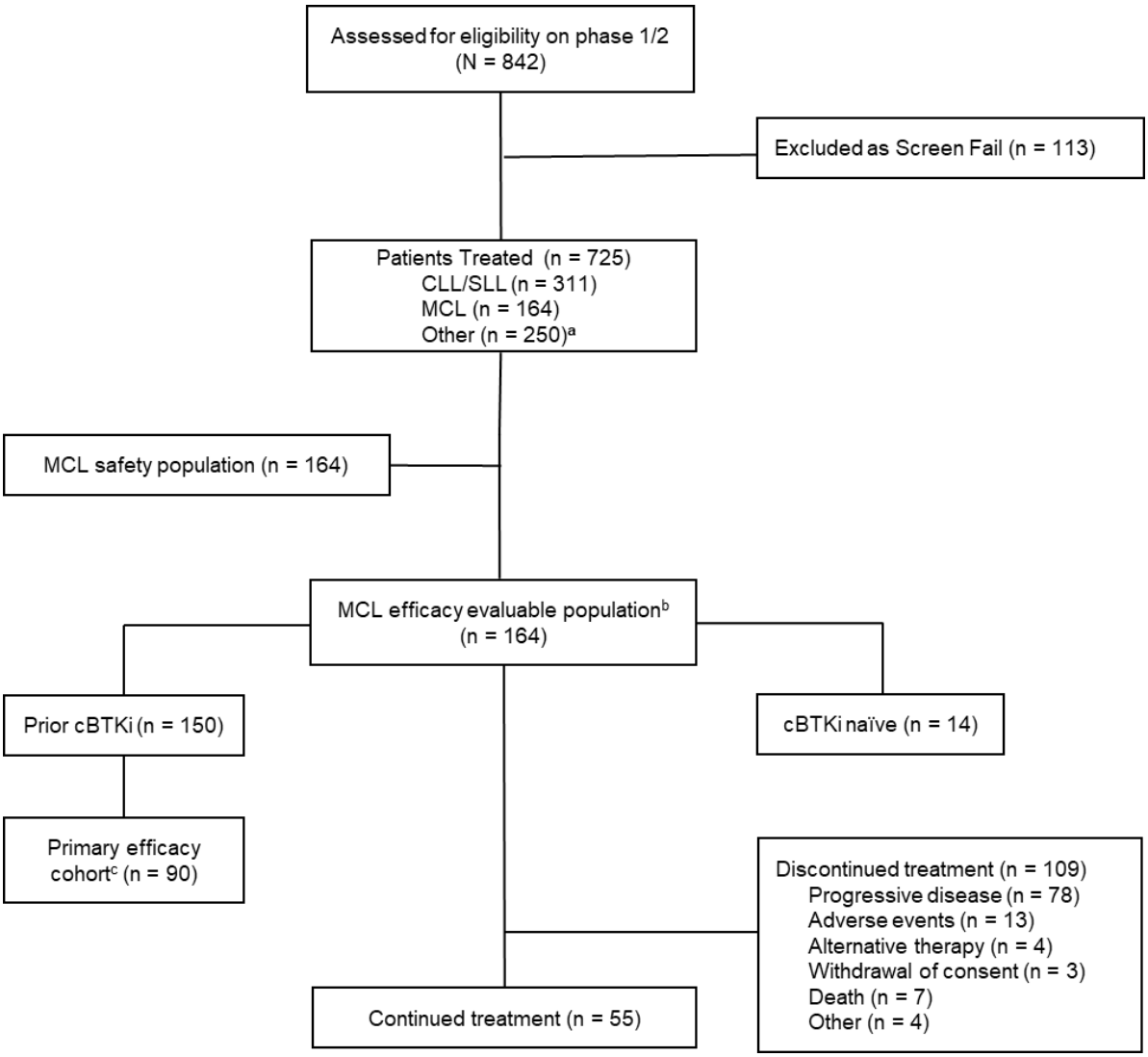
	MCL safety population (n=164)	Overall safety population (N=725)
Any TRAE leading to treatment discontinuation	5 (3.0)	15 (2.1)
Alopecia	1 (0.1)	1 (0.1)
Anemia	0	1 (0.1)
COVID-19 pneumonia	0	1 (0.1)
Cholecystitis	1 (0.1)	1 (0.1)
Fatigue	1 (0.1)	1 (0.1)
Febrile neutropenia	0	1 (0.1)
Myalgia	0	1 (0.1)
Myelodysplastic syndrome	0	1 (0.1)
Neuropathy peripheral	0	1 (0.1)
Neutropenia	1 (0.1)	1 (0.1)
Neutrophil count decreased	1 (0.1)	1 (0.1)
Pneumonitis	1 (0.1)	1 (0.1)
Rash maculo-papular	0	1 (0.1)
Respiratory failure	0	1 (0.1)
Septic shock	0	1 (0.1)
Staphylococcal sepsis	0	1 (0.1)
Weight decreased	1 (0.1)	1 (0.1)

Table S5. Efficacy of pirtobrutinib in patients with BTKi as their most recent prior line of therapy.

	PAS with BTKi As Most Recent Prior Systemic Therapy (N = 55)	**Other (N = 35)**
Overall Response Rate (ORR)		
n (%)	29 (52.7)	23 (65.7)
95% Confidence Interval [1]	38.8, 66.3	47.8, 80.9
Best overall response, n (%)		
Complete Response (CR)	7 (12.7)	11 (31.4)
Partial Response (PR)	22 (40.0)	12 (34.3)
Stable Disease (SD)	9 (16.4)	5 (14.3)
Progressive Disease (PD)	10 (18.2)	5 (14.3)
Not Evaluable (NE)	7 (12.7)	2 (5.7)
Duration of Response		
Median duration of response, mo (95% CI)	14.82 (5.55, NE)	21.59 (6.47, NE)
Patients with a response, n	29	23
Median follow up, mo	8.21	12.98

Supplemental Figures.

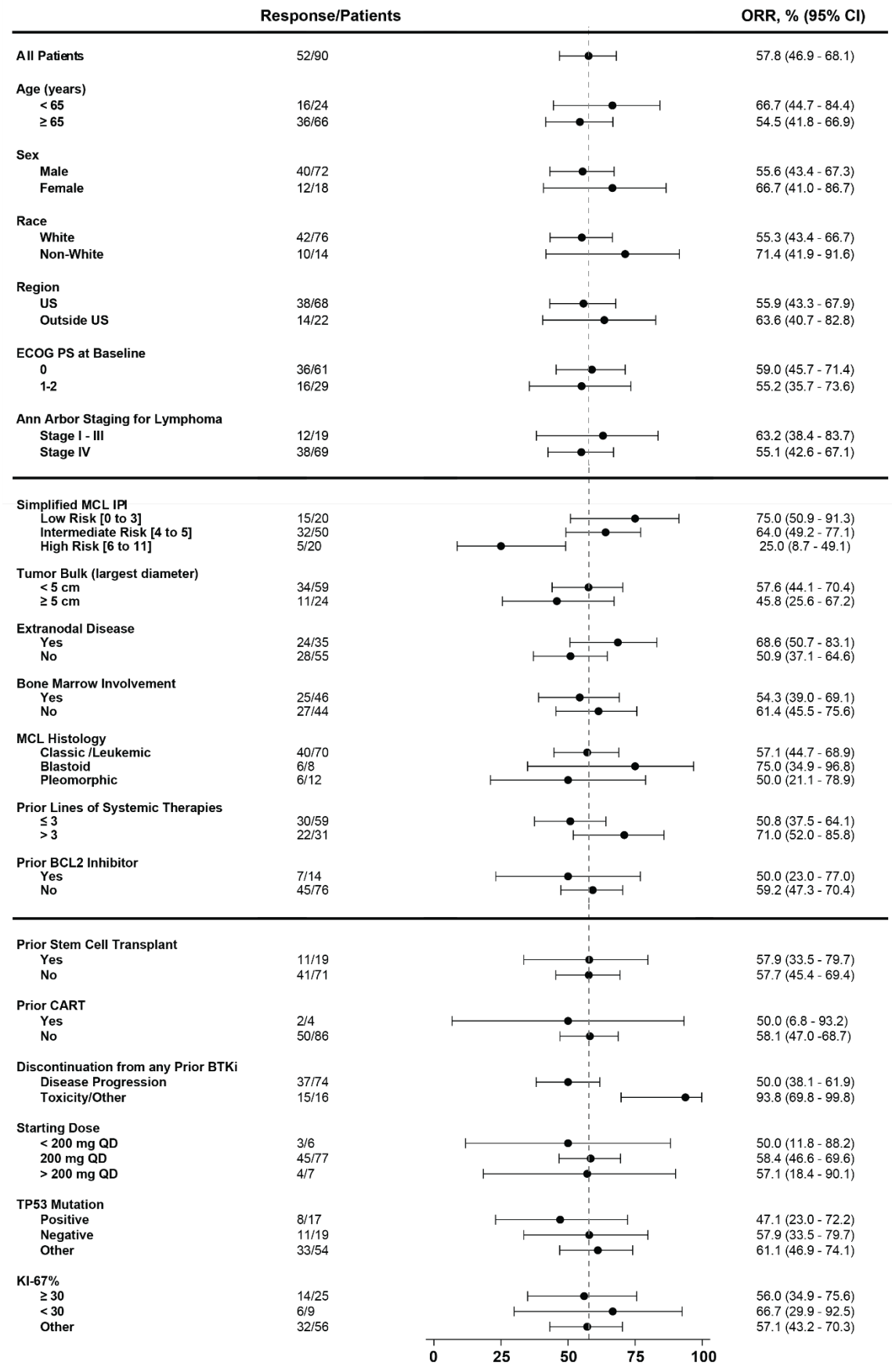
Figure S1. CONSORT diagram of patient disposition from the phase 1/2 BRUIN trial.



[a]Other includes DLBCL, WM, FL, MZL, Richter transformation, B-PLL, Hairy Cell Leukemia, PCNSL, and other transformation. [b]Efficacy evaluable patients are those who had at least one post-baseline response assessment or had discontinued treatment prior to first post-baseline response assessment.

[c]The primary efficacy cohort included the first 90 MCL patients enrolled to either phase 1 or 2 who had measurable disease per investigator, had received a prior cBTKi containing regimen, and had no known central nervous system involvement.

Figure S2. Overall response rate to pirtobrutinib in cBTKi pre-treated MCL subgroups.



Data reported in the forest plot is overall response rate among prespecified patient characteristic subgroups. Two-sided 95% CI was calculated using the exact binomial distribution. Three patients received a phase one starting dose of 25mg, two patients received a starting dose of 100mg, one patient received a starting dose of 150mg, two patients received a starting dose of 250mg, and five patients received a starting dose of 300mg. [a]Reason for cBTKi discontinuation was calculated as percent of patients who received prior cBTKi for either progression or toxicity/other. [b]In the event more than one reason was noted for discontinuation, disease progression took priority. [c]mDOR was 14.8 months (95% CI, 5.5 - not reached) for patients in the primary efficacy cohort who discontinued prior cBTKi due to disease progression. ECOG, Eastern Cooperative Oncology Group; MCL, mantle cell lymphoma; cBTKi, covalent Bruton tyrosine kinase inhibitor; CI, confidence interval.

Figure S3. Kaplan-Meier plot of duration of response in cBTKi naïve MCL patients treated with pirtobrutinib

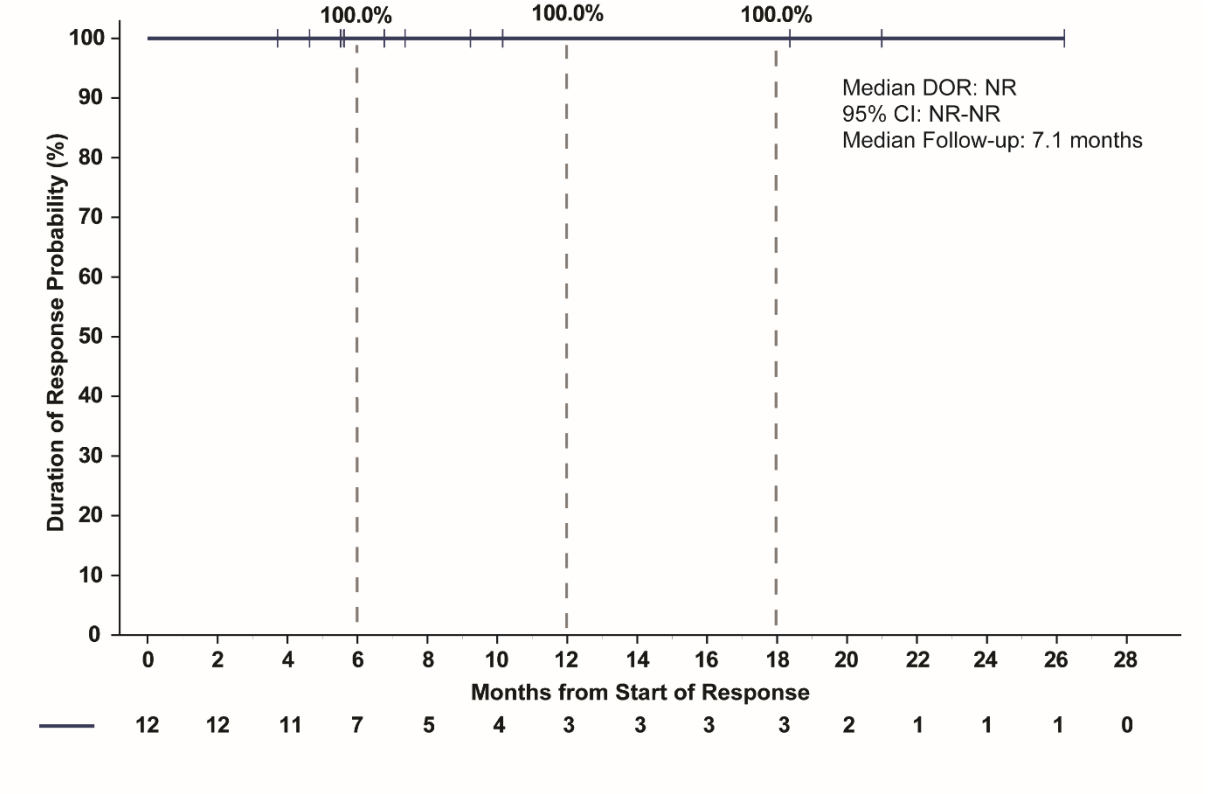


Figure S4. Kaplan-Meier plot of progression-free survival in cBTKi naïve MCL patients treated with pirtobrutinib

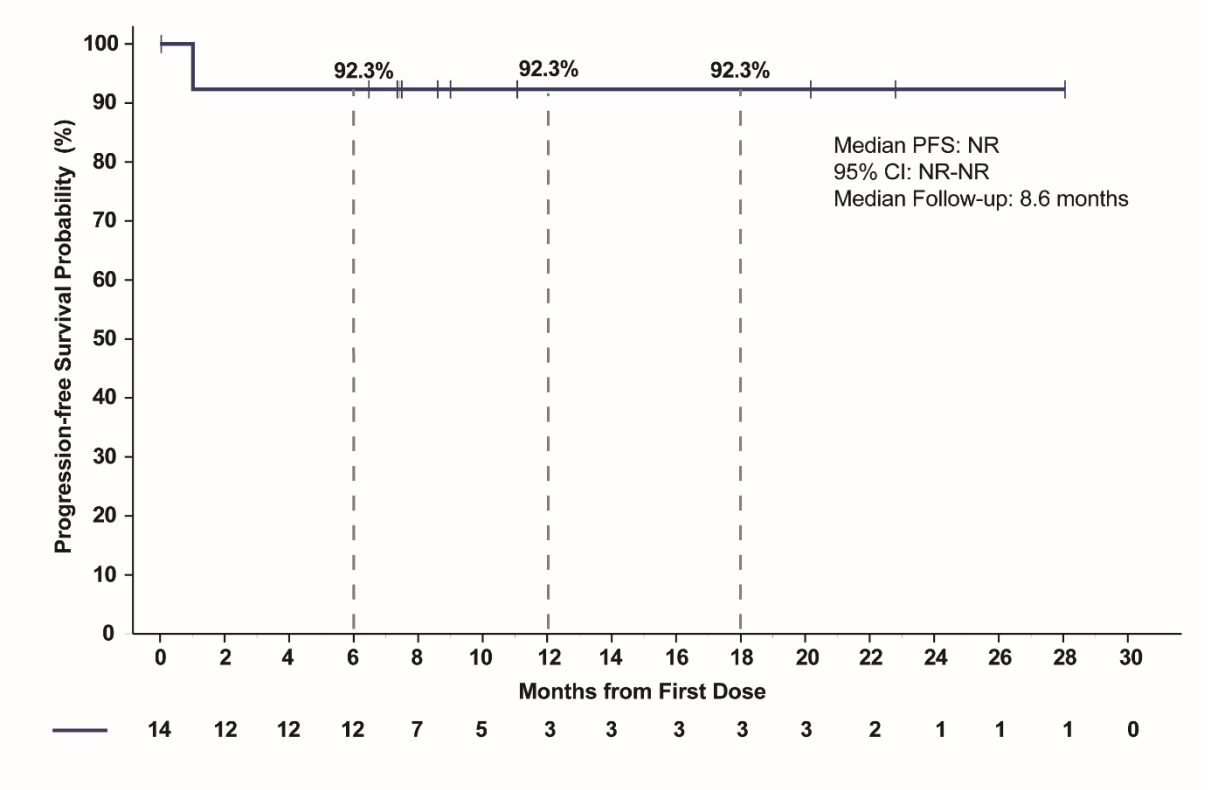
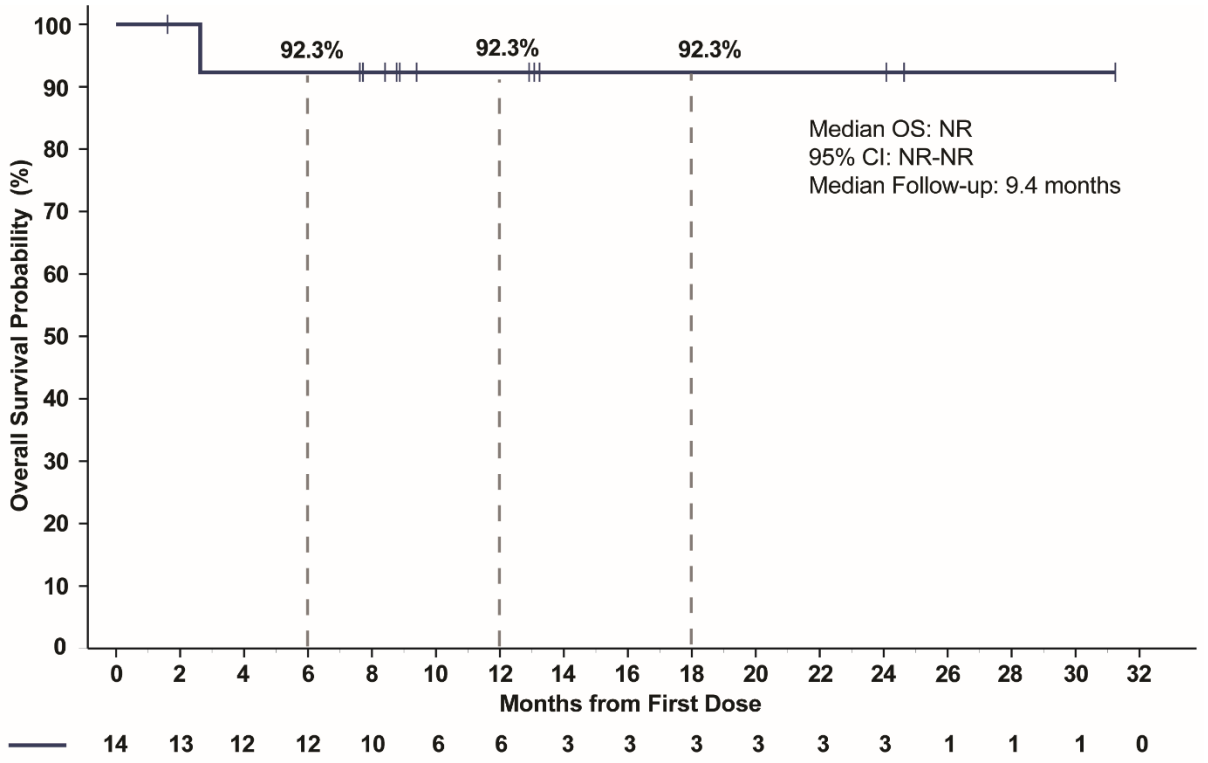


Figure S5. Kaplan-Meier plot of overall survival in cBTKi naïve MCL patients treated with pirtobrutinib



References

1. Owen C, Berinstein NL, Christofides A, et al: Review of Bruton tyrosine kinase inhibitors for the treatment of relapsed or refractory mantle cell lymphoma. Current oncology (Toronto, Ont.) 26:e233-e240, 2019
2. Seiler T, Dreyling M: Bruton's tyrosine kinase inhibitors in B-cell lymphoma: current experience and future perspectives. Expert Opin Investig Drugs 26:909-915, 2017
3. Martin P, Maddocks K, Leonard JP, et al: Postibrutinib outcomes in patients with mantle cell lymphoma. Blood 127:1559-63, 2016
4. Jain P, Kanagal-Shamanna R, Zhang S, et al: Long-term outcomes and mutation profiling of patients with mantle cell lymphoma (MCL) who discontinued ibrutinib. Br J Haematol 183:578-587, 2018
5. Epperla N, Hamadani M, Cashen AF, et al: Predictive factors and outcomes for ibrutinib therapy in relapsed/refractory mantle cell lymphoma-a "real world" study. Hematol Oncol 35:528-535, 2017
6. Shah B, Zhao X, Silva AS, et al: Resistance to Ibrutinib in B Cell Malignancies: One Size Does Not Fit All. Trends Cancer 4:197-206, 2018
7. Cheah CY, Chihara D, Romaguera JE, et al: Patients with mantle cell lymphoma failing ibrutinib are unlikely to respond to salvage chemotherapy and have poor outcomes. Ann Oncol 26:1175-1179, 2015
8. Rai S, Tanizawa Y, Cai Z, et al: Outcomes for Recurrent Mantle Cell Lymphoma Post-Ibrutinib Therapy: A Retrospective Cohort Study from a Japanese Administrative Database. Adv Ther 39:4792-4807, 2022
9. Hess G, Dreyling M, Oberic L, et al: Real-world experience among patients with relapsed/refractory mantle cell lymphoma after Bruton tyrosine kinase inhibitor failure in Europe: The SCHOLAR-2 retrospective chart review study. British Journal of Haematology n/a
10. Wang M, Munoz J, Goy A, et al: KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma. N Engl J Med 382:1331-1342, 2020
11. Sharma S, Galanina N, Guo A, et al: Identification of a structurally novel BTK mutation that drives ibrutinib resistance in CLL. Oncotarget 7:68833-68841, 2016
12. Shaffer AL, 3rd, Phelan JD, Wang JQ, et al: Overcoming Acquired Epigenetic Resistance to BTK Inhibitors. Blood Cancer Discov 2:630-647, 2021
13. Chiron D, Di Liberto M, Martin P, et al: Cell-cycle reprogramming for PI3K inhibition overrides a relapse-specific C481S BTK mutation revealed by longitudinal functional genomics in mantle cell lymphoma. Cancer Discov 4:1022-35, 2014
14. Thompson ER, Nguyen T, Kankanige Y, et al: Single-cell sequencing demonstrates complex resistance landscape in CLL and MCL treated with BTK and BCL2 inhibitors. Blood Adv 6:503-508, 2022
15. Tiemann M, Schrader C, Klapper W, et al: Histopathology, cell proliferation indices and clinical outcome in 304 patients with mantle cell lymphoma (MCL): a clinicopathological study from the European MCL Network. Br J Haematol 131:29-38, 2005
16. Wang M, Rule S, Zinzani PL, et al: Durable response with single-agent acalabrutinib in patients with relapsed or refractory mantle cell lymphoma. Leukemia 33:2762-2766, 2019
17. Tam CS, Opat S, Simpson D, et al: Zanubrutinib for the treatment of relapsed or refractory mantle cell lymphoma. Blood Adv 5:2577-2585, 2021
18. Rule S, Dreyling M, Goy A, et al: Ibrutinib for the treatment of relapsed/refractory mantle cell lymphoma: extended 3.5-year follow up from a pooled analysis. Haematologica 104:e211-e214, 2019

19. Mato AR, Shah NN, Jurczak W, et al: Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. The Lancet 397:892-901, 2021
20. Cheson BD, Fisher RI, Barrington SF, et al: Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 32:3059-68, 2014
21. Van Heertum RL, Scarimbolo R, Wolodzko JG, et al: Lugano 2014 criteria for assessing FDG-PET/CT in lymphoma: an operational approach for clinical trials. Drug Des Devel Ther 11:1719-1728, 2017
22. Hess G, Smith SM, Berkenblit A, et al: Temsirolimus in Mantle Cell Lymphoma and Other Non-Hodgkin Lymphoma Subtypes. Seminars in Oncology 36:S37-S45, 2009
23. Fisher RI, Bernstein SH, Kahl BS, et al: Multicenter Phase II Study of Bortezomib in Patients With Relapsed or Refractory Mantle Cell Lymphoma. Journal of Clinical Oncology 24:4867-4874, 2006
24. Goy A, Kalayoglu Besisik S, Drach J, et al: Longer-term follow-up and outcome by tumour cell proliferation rate (Ki-67) in patients with relapsed/refractory mantle cell lymphoma treated with lenalidomide on MCL-001(EMERGE) pivotal trial. Br J Haematol 170:496-503, 2015
25. Eyre TA, Walter HS, Iyengar S, et al: Efficacy of venetoclax monotherapy in patients with relapsed, refractory mantle cell lymphoma after Bruton tyrosine kinase inhibitor therapy. Haematologica 104:e68-e71, 2019
26. Byrd JC, Hillmen P, Ghia P, et al: Acalabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia: Results of the First Randomized Phase III Trial. Journal of Clinical Oncology 39:3441-3452, 2021
27. Pharmacyclics. (2018).Imbruvica (ibrutinib) package insert.
28. BeiGene USA Inc. (2019).Brukinsa (zanubrutinib) package insert.
29. Sharman JP, Egyed M, Jurczak W, et al: Acalabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naive chronic lymphocytic leukaemia (ELEVATE-TN): a randomised, controlled, phase 3 trial. The Lancet 395:1278-1291, 2020
30. Maeve A O'Reilly RS, William Wilson, David Burns, Caroline Besley, Thomas Creasey, Ben Uttenthal, Johnathon Elliot, Claire Roddie, Andrea Kuhnl, Shankara Paneesha, Frances Seymour, Sunil Iyengar, Lourdes Rubio, Matthew Wilson, Stephen Boyle, Kathleen PL Cheok, Graham P. Collins, Rod Johnson and Andrew K. McMillan: Brexucabtagene Autoleucel for Relapsed/Refractory Mantle Cell Lymphoma: Real-World Outcomes in the United Kingdom.
31. Jain T, Bar M, Kansagra AJ, et al: Use of Chimeric Antigen Receptor T Cell Therapy in Clinical Practice for Relapsed/Refractory Aggressive B Cell Non-Hodgkin Lymphoma: An Expert Panel Opinion from the American Society for Transplantation and Cellular Therapy. Biol Blood Marrow Transplant 25:2305-2321, 2019
32. Phillips TJ, Dickinson M, Morschhauser F, et al: Glofitamab Monotherapy Induces High Complete Response Rates in Patients with Heavily Pretreated Relapsed or Refractory Mantle Cell Lymphoma. Blood 140:178-180, 2022
33. Woyach JA, Flinn IW, Awan FT, et al: Preliminary Efficacy and Safety of MK-1026, a Non-Covalent Inhibitor of Wild-Type and C481S Mutated Bruton Tyrosine Kinase, in B-Cell Malignancies: A Phase 2 Dose Expansion Study. Blood 138:392-392, 2021
34. Eyre TA, Shah NN, Dreyling M, et al: BRUIN MCL-321: phase III study of pirtobrutinib versus investigator choice of BTK inhibitor in BTK inhibitor naïve mantle cell lymphoma. Future Oncology 0:null