Real-World Outcomes of Brexucabtagene Autoleucel for Relapsed or Refractory Mantle Cell Lymphoma: A CIBMTR Subgroup Analysis of High-Risk Characteristics

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Background

- In the 3-year update of the pivotal ZUMA-2 study of brexu-cel treatment in patients with R/R MCL, ORR was 91% (CR rate, 68%), median OS was 46.6 months, and median PFS was 25.8 months[1]
  - Outcomes were comparable across high-risk patient subgroups
- Brexu-cel treatment for R/R MCL has also been evaluated in the real-world setting[2]
  - In an analysis of real-world patients with R/R MCL, ORR was 89% (CR rate, 78%), 1-year OS was 74%, and 1-year PFS was 61%
  - Outcomes were consistent regardless of prior treatment, including BTKi or bendamustine
- High-risk features, such as *TP53* aberrations and high Ki-67, have been associated with poor outcomes among patients with R/R MCL treated with brexu-cel, although not in an adjusted analysis[3]
- Here, we evaluated the effectiveness and safety outcomes of brexu-cel to treat R/R MCL in a real-world setting by high-risk features (del of *TP53*/17p and Ki-67 ≥50%) and by ZUMA-2 eligibility[1]

1. Wang M, et al. *J Clin Oncol*. 2023;41:555-567. 2. Kambhampati S, et al. *J Clin Oncol.* 2023;41(16_suppl):7507. 3. Wang Y, et al. *J Clin Oncol.* 2023;41:2594-2606.
Brexu-cel, brexucabtagene autoleucel; BTKi, Bruton tyrosine kinase inhibitor; CR, complete response; del of *TP53*/17p, *TP53* deletion or 17p deletion; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R/R MCL, relapsed/refractory mantle cell lymphoma.

Study Design and Analysis

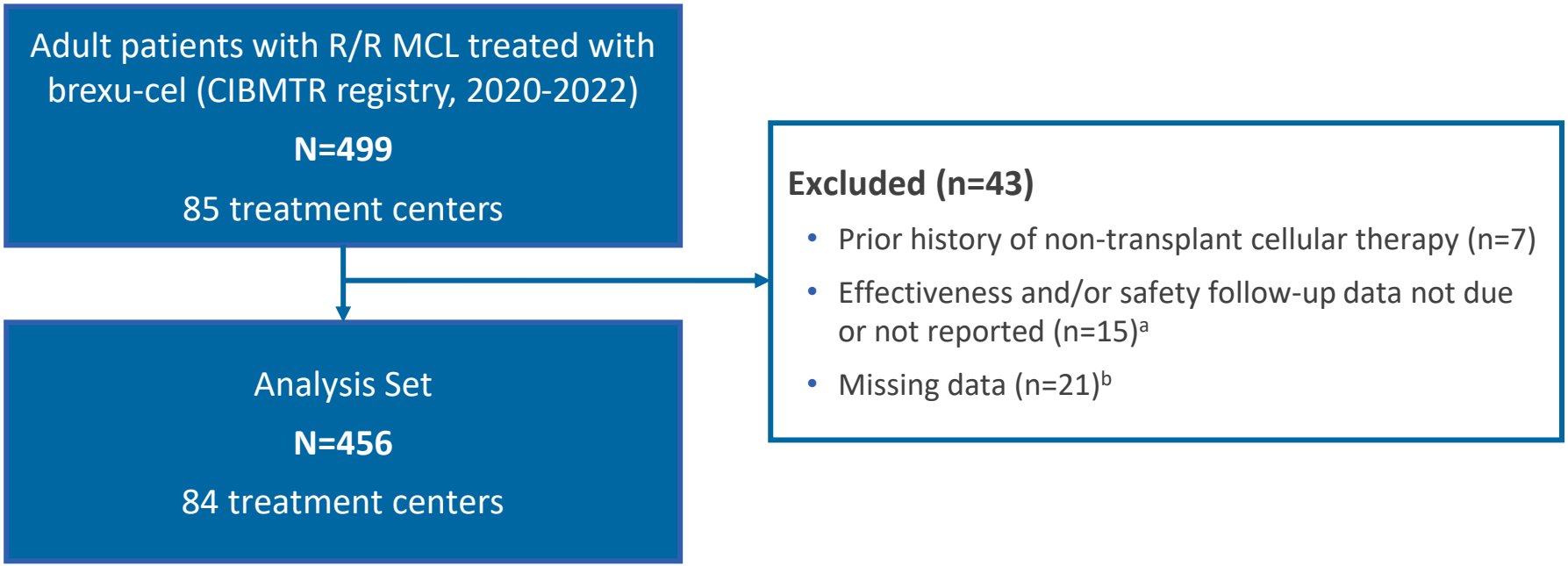
Registry-Based Non-interventional Cohort Study	• Data were prospectively collected as part of a PASS through the **CIBMTR® registry** and included patients with R/R MCL treated with FDA-approved brexu-cel in the United States from July 2020 through December 2022[a] • Data cutoff: **June 21, 2023[b]** • Median follow-up: **12.3 months (range, 2.9-28.6)**
Outcomes of Interest	• **Effectiveness[c]:** ORR, CR rate, DOR, OS, PFS, REL/PD • **Safety[c]:** CRS,[d] ICANS,[d] prolonged neutropenia and thrombocytopenia, NRM, infection • Outcomes were evaluated in patients who completed 100-day follow-up reporting
Statistical Analysis	• Univariate analyses were performed with descriptive statistics herein • **Logistic and Cox regressions** were employed to estimate effect of high-risk features, accounting for other factors

[a] Accrual of n=499 adult patients treated with brexu-cel for R/R MCL. [b] Patients who died or discontinued prior to data cutoff were also included. [c] Center-reported. [d] ASTCT consensus grading criteria.[1]

1. Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25:625-638.

ASTCT, American Society of Transplantation and Cellular Therapy; brexu-cel, brexucabtagene autoleucel; CIBMTR, Center for International Blood and Marrow Transplant Research; CR, complete response; CRS, cytokine release syndrome; DOR, duration of response; FDA, US Food and Drug Administration; ICANS, immune effector cell-associated neurotoxicity syndrome; NRM, non-relapse mortality; ORR, overall response rate; OS, overall survival; PASS, post-authorization safety study; PFS, progression-free survival; R/R MCL, relapsed/refractory mantle cell lymphoma; REL/PD, relapse or progressive disease.

Study Cohort and Patient Disposition



[a] Patients without 100-day follow-up reporting were excluded (n=15). [b] Patients excluded due to incomplete baseline data (n=19) and/or missing data on prior treatment (n=22).
Brexu-cel, brexucabtagene autoleucel; CIBMTR, Center for International Blood and Marrow Transplant Research; R/R MCL, relapsed/refractory mantle cell lymphoma.

Baseline Patient Characteristics

Characteristics,[a] n (%)	*TP53*/17p		Ki-67		ZUMA-2 Eligibility		Overall (N=456)
	Deletion (n=44)	No deletion (n=183)	≥50% (n=146)	<50% (n=111)	Ineligible (n=262)	Eligible (n=194)	
Age, median (range), years	**63 (47–80)**	**67 (34–82)**	66 (36–83)	66 (34–82)	67 (38–84)	65 (34–83)	67 (34–84)
Age ≥65 years	**18 (41)**	**112 (61)**	84 (58)	64 (58)	170 (65)	106 (55)	276 (61)
ECOG PS ≥2 prior to infusion[b]	3 (9)	7 (4)	10 (8)	4 (4)	**24 (10)**	**0**	24 (6)
Clinically significant comorbidities[b,c]	33 (75)	138 (76)	113 (78)	89 (82)	**229 (87)**	**115 (61)**	344 (76)
Disease stage at diagnosis III-IV[b]	37 (100)	143 (89)	120 (92)	92 (92)	200 (91)	137 (90)	337 (91)
Elevated LDH at diagnosis[b,d]	18 (58)	52 (49)	**38 (41)**	**44 (57)**	66 (47)	51 (47)	117 (47)
Chemoresistant prior to infusion[b,e]	**35 (81)**	**109 (66)**	87 (66)	78 (74)	**179 (76)**	**116 (64)**	295 (71)
Lines of prior therapy, median (range)[f]	3 (1–7)	3 (1–11)	3 (1–11)	3 (1–12)	3 (1–12)	4 (1–10)	3 (1–12)
Prior HCT	**5 (12)**	**55 (30)**	45 (31)	28 (26)	85 (32)	62 (32)	147 (32)
Prior BTKi exposure[b]	36 (82)	157 (86)	**118 (81)**	**102 (92)**	**205 (78)**	**194 (100)**	397 (87)
Bridging therapy (any type)[b]	21 (48)	71 (40)	**53 (37)**	**56 (52)**	103 (41)	90 (48)	193 (44)
Planned outpatient infusion	1 (2)	19 (10)	8 (5)	9 (8)	21 (8)	19 (10)	40 (9)

- Of the evaluable patients in this real-world population, 42% had del of *TP53*/17p and/or Ki-67 ≥50%[b]
- Additionally, 57% of patients would **not** have met ZUMA-2 eligibility, mostly due to the presence of comorbidities prior to infusion

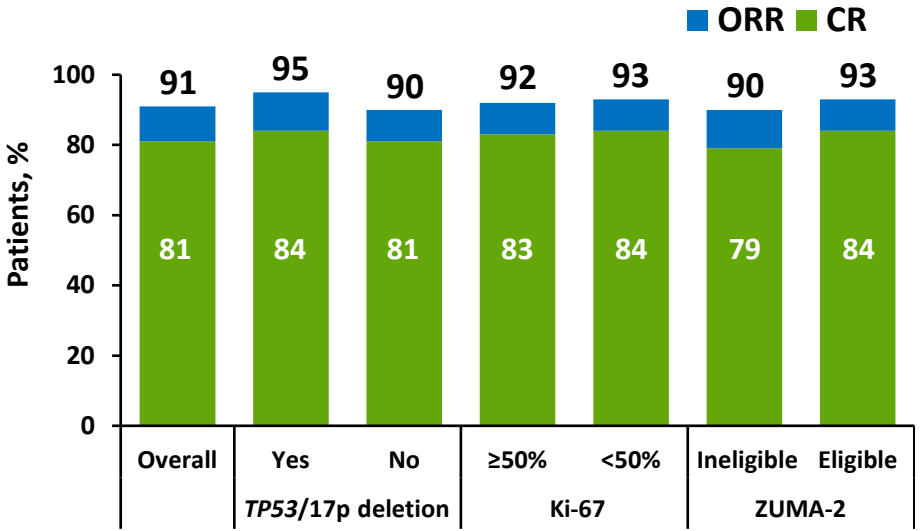
[a] In the overall population, 76% of patients were male, 33% had elevated LDH prior to infusion, 77% had received ≥3 lines of prior therapy, and median time from leukapheresis to infusion was 28 days. There were relatively small to no differences in these variables between the respective subgroups shown here. Fisher exact test and Wilcoxon rank sum test were used to assess statistical significantly differences in baseline characteristics.
[b] Percentages are based on the number of patients with available data. [c] Comorbidities were defined per the HCT-CI[1] and included severe underweight as body mass index <20.5. [d] Elevated LDH defined as LDH greater than center's ULN. [e] Chemoresistance was defined as patients who had stable or progressive disease prior to infusion. [f] Excluding HCT.

1. Sorror ML, et al. *Blood*. 2005;106:2912-2919.

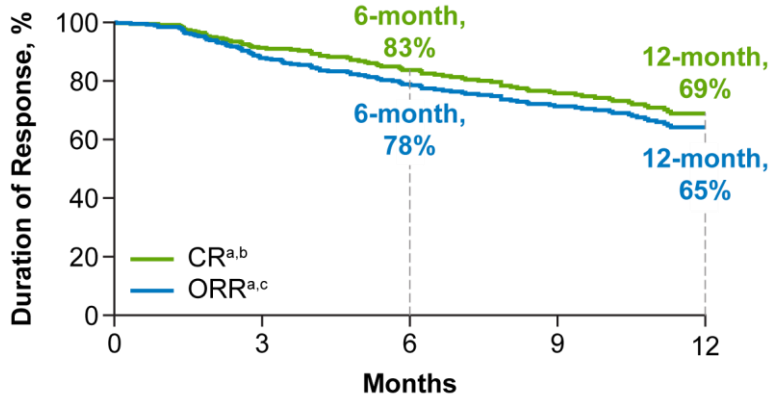
BTKi, Bruton tyrosine kinase inhibitor; del of *TP53*/17p, *TP53* deletion or 17p deletion; ECOG PS, Eastern Cooperative Oncology Group performance status; HCT, hematopoietic cell transplant; HCT-CI, hematopoietic cell transplant-comorbidity index; LDH, lactate dehydrogenase; ULN, upper limit of normal.

ORR, CR Rate, and DOR Among all Patients

ORR and CR Rate



Kaplan-Meier Estimates for DOR



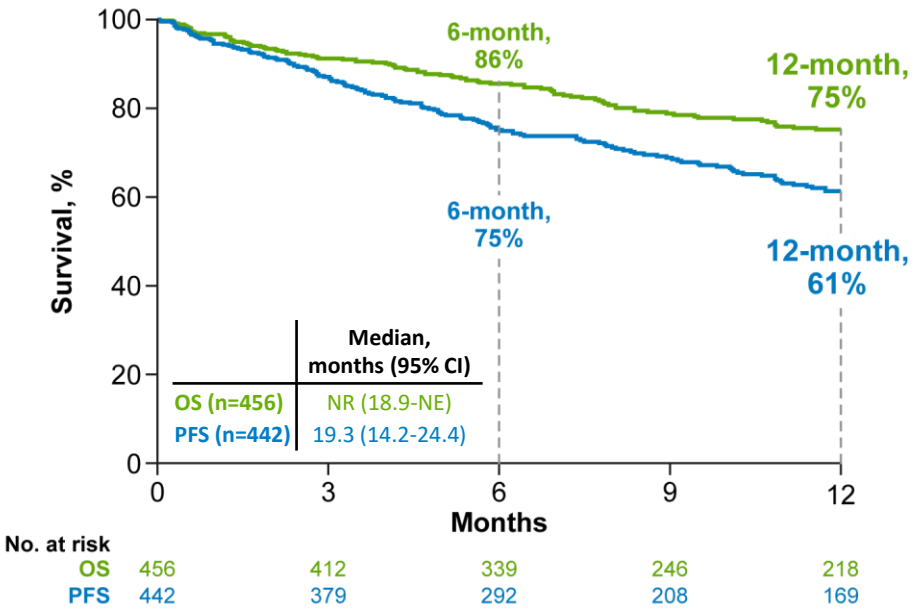
No. at risk					
Patients with CR	347	290	209	168	71
Patients with ORR	388	311	219	176	75

- ORR and CR rates were consistent across high-risk subgroups
- Median DOR was not yet reached

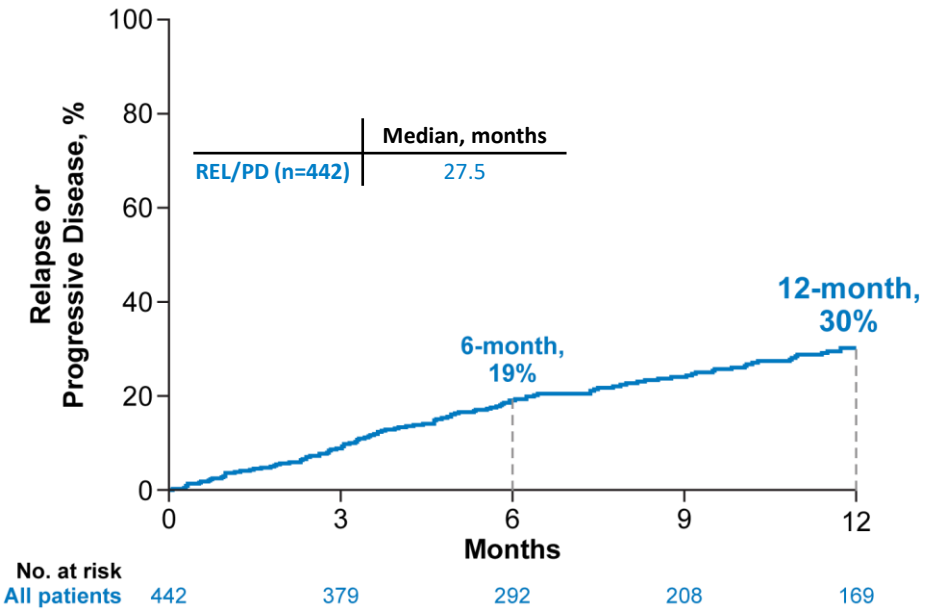
[a] Subsequent cellular therapy and HCT without previously documented relapse or disease progression were censored; median follow-up was 12.3 months (range, 2.9-28.6). [b] Among patients who achieved CR as best response.
[c] Among patients who achieved CR/PR as best response.
CR, complete response; DOR, duration of response; HCT, hematopoietic cell transplant; ORR, overall response rate; PR, partial response.

PFS, OS, and Relapses Among all Patients

Kaplan-Meier Estimates of PFS[a,b] and OS[b]



Cumulative Incidence of REL/PD[a,b]



- PFS and OS rates at 12 months in the ZUMA-2 primary analysis were 61% and 83%, respectively[1]

[a] Subsequent cellular therapy and HCT without previously documented relapse or disease progression were censored. [b] Median follow-up was 12.3 months (range, 2.9-28.6).

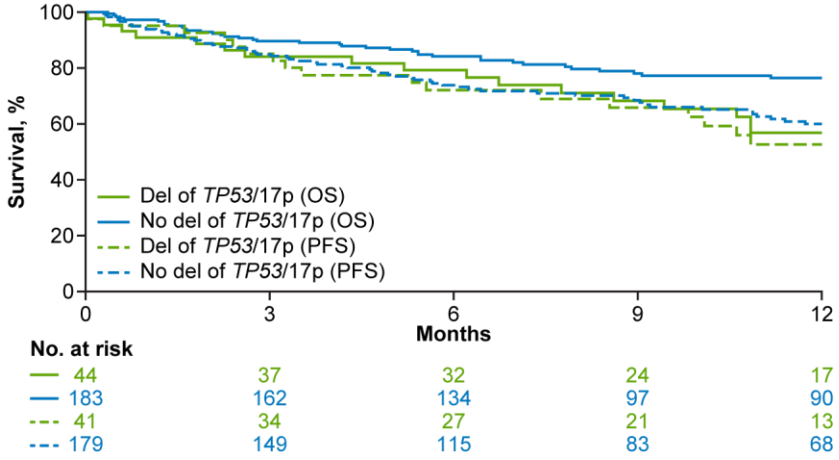
1. Wang M, et al. *N Engl J Med*. 2020;382:1331-1342.

HCT, hematopoietic cell transplant; NE, not evaluable; NR, not reached; OS, overall survival; PFS, progression-free survival; REL/PD, relapse or progressive disease.

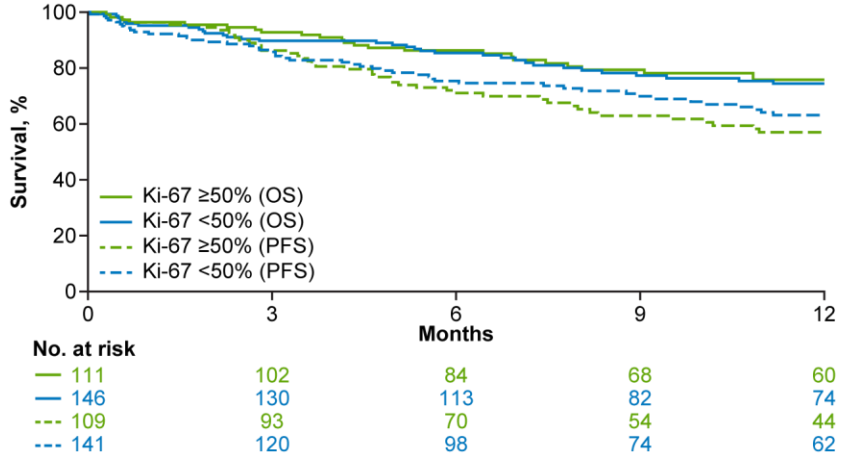
OS and PFS by Del of *TP53*/17p, Ki-67, and ZUMA-2 Eligibility

Outcomes	*TP53*/17p		Ki-67		ZUMA-2 Eligibility	
	Deletion (n=44)	No deletion (n=183)	≥50% (n=146)	<50% (n=111)	Ineligible (n=262)	Eligible (n=194)
OS 12-month rate, % (95% CI)	57 (40-71)	76 (69-82)	74 (66-81)	76 (66-83)	75 (69-81)	75 (68-81)
PFS 12-month rate, % (95% CI)	53 (35-68)	60 (51-67)	63 (54-71)	57 (46-66)	58 (50-64)	66 (58-73)

PFS and OS by Del of *TP53*/17p



PFS and OS by Ki-67

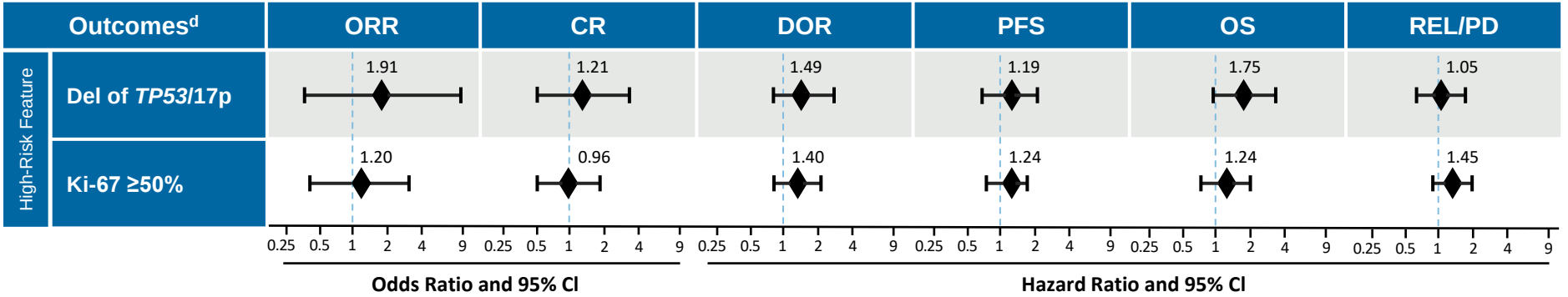


- No statistically significant differences in OS and PFS at any time point between all high-risk subgroups in univariate analyses

Del of *TP53*/17p, *TP53* deletion or 17p deletion; OS, overall survival; PFS, progression-free survival.

Effectiveness Outcomes With Multivariable Adjustment

Adjusted ORR, CR, DOR, PFS, OS, and REL/PD[a-d]

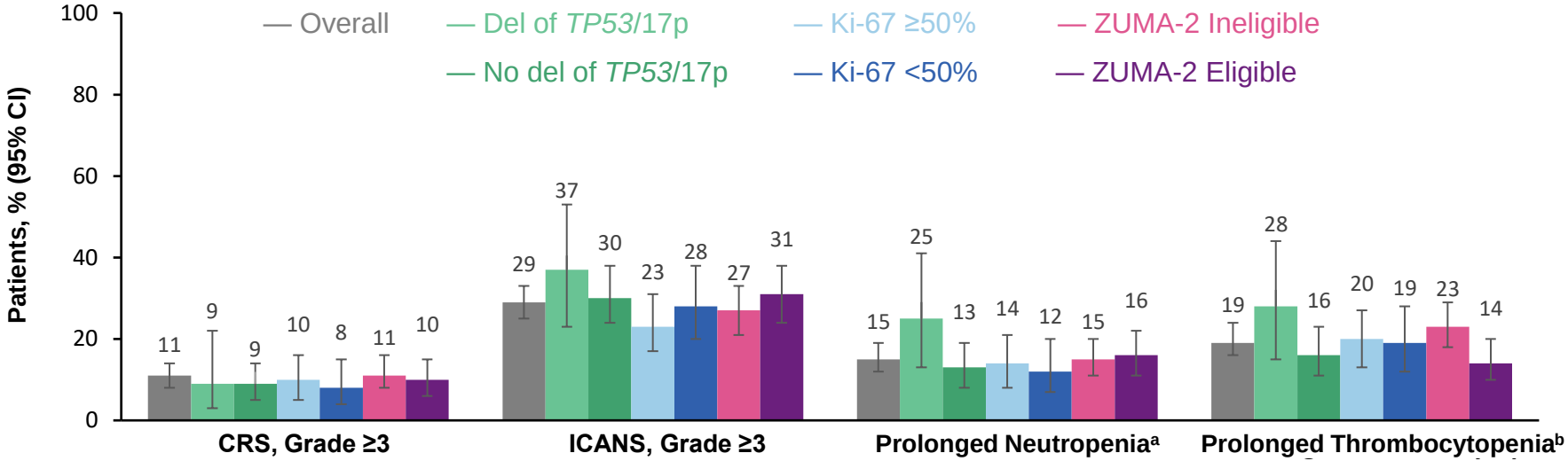


- After multivariable adjustment, the effectiveness of brexu-cel in patients with del of *TP53*/17p and/or Ki-67 ≥50% was consistent with patients who did not have those high-risk features

[a] A stepwise selection at $P<0.2$ was used to select covariates for the multivariate models; candidate variables were age, sex, race/ethnicity, ECOG PS prior to infusion, elevated LDH above ULN prior to infusion, white blood cell count prior to infusion, extranodal involvement at diagnosis or prior to infusion, chemo-sensitivity prior to infusion, number of prior lines of therapy (not counting prior HCT), bridging therapy, intention to treat in outpatient setting, time from leukapheresis to infusion, year of infusion, and each of the following comorbidities: hepatic (moderate/severe), renal (moderate/severe), pulmonary (moderate/severe), cardiac or cerebrovascular disease or heart valve disease, infection requiring antimicrobial treatment, inflammatory bowel/rheumatologic disease, prior cancer (except non-melanoma skin cancer), and arrhythmia). [b] DOR, PFS, OS, REL/PD based on direct adjusted survival estimates from a stratified Cox model. [c] X-axis measured on logarithmic scale. [d] Adjusted HRs for DOR, PFS, OS, REL/PD; adjusted ORs for ORR, CR.

Brexu-cel, brexucabtagene autoleucel; CR, complete response; del of *TP53*/17p, *TP53* deletion or 17p deletion; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HCT, hematopoietic cell transplant; HR, hazard ratio; LDH, lactate dehydrogenase; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; REL/PD, relapse or progressive disease; ULN, upper limit of normal.

Safety Outcomes by High-Risk Features

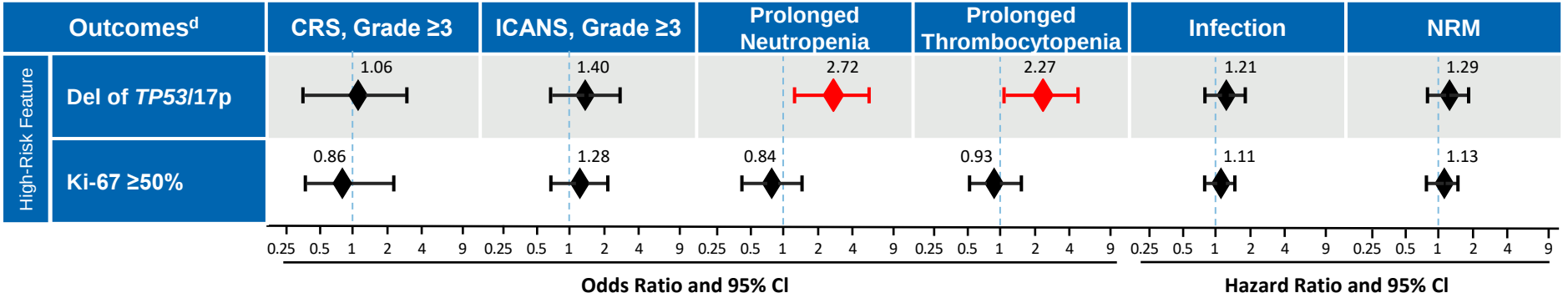


- Grade ≥3 CRS[c] and ICANS[c] were observed in 11% (95% CI, 8-14) and 29% (95% CI, 25-33) of patients in the overall population, respectively
- NRM was consistent across subgroups, and NRM at Year 1 was 8% (data not shown)
- Incidence of safety outcomes did not vary significantly across high-risk subgroups

[a] Prolonged neutropenia was defined as failure to recover absolute neutrophil count ≥500/mm^3 and sustain 3 lab values within the first 30 days after infusion. [b] Prolonged thrombocytopenia was defined as failure to recover platelet count ≥20×10^9/L within the first 30 days after infusion. [c] CRS and ICANS were graded according to ASTCT Consensus Criteria.
ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; del of *TP53*/17p, *TP53* deletion or 17p deletion; ICANS, immune effector cell-associated neurotoxicity syndrome; NRM, non-relapse mortality.

Safety Outcomes With Multivariable Adjustment

Adjusted CRS, ICANS, Prolonged Cytopenia, Infection, and NRM[a-d]



- After multivariable adjustment, all safety outcomes were comparable between patients with Ki-67 ≥50% and <50%
- Regardless of del of *TP53*/17p status, incidence of Grade ≥3 CRS, Grade ≥3 ICANS, infections, and NRM were comparable[d]

[a] A stepwise selection at $P<0.2$ was used to select covariates for the multivariate models; candidate variables were age, sex, race/ethnicity, ECOG PS prior to infusion, elevated LDH above ULN prior to infusion, white blood cell count prior to infusion, extranodal involvement at diagnosis or prior to infusion, chemo-sensitivity prior to infusion, number of prior lines of therapy (not counting prior HCT), bridging therapy, intention to treat in outpatient setting, time from leukapheresis to infusion, year of infusion, and each of the following comorbidities: hepatic (moderate/severe), renal (moderate/severe), pulmonary (moderate/severe), cardiac or cerebrovascular disease or heart valve disease, infection requiring antimicrobial treatment, inflammatory bowel/rheumatologic disease, prior cancer (except non-melanoma skin cancer), and arrhythmia. [b] Infections and NRM based on direct adjusted survival estimates from a stratified Cox model. [c] X-axis measured on logarithmic scale. [d] Adjusted cause-specific HRs for infection and NRM; adjusted ORs for CRS Grade ≥3, ICANS Grade ≥3, prolonged neutropenia and prolonged thrombocytopenia.

CRS, cytokine release syndrome; del of *TP53*/17p, *TP53* deletion or 17p deletion; ECOG PS, Eastern Cooperative Oncology Group performance status; HCT, hematopoietic cell transplant; HR, hazard ratio; ICANS, immune effector cell-associated neurotoxicity syndrome; LDH, lactate dehydrogenase; NRM, non-relapse mortality; OR, odds ratio; ULN, upper limit of normal.

Conclusions

- These real-world findings suggest that effectiveness outcomes of brexu-cel treatment are largely consistent regardless of high-risk features, specifically del of *TP53*/17p or Ki-67 ≥50%, or ZUMA-2 eligibility
  - However, patients without del of *TP53*/17p appeared to have numerically longer OS than patients with del of *TP53*/17p
- Most safety outcomes were also comparable regardless of the presence of high-risk features
  - Patients with del of *TP53*/17p were more likely to have prolonged neutropenia and prolonged thrombocytopenia than those without del of *TP53*/17p
- A limitation of this analysis includes the lack of data availability, specifically regarding *TP53* mutations
- This is the largest real-world brexu-cel study to date and further supports the use of brexu-cel as the standard of care across a diverse patient population with R/R MCL, including those with high-risk features

Brexu-cel, brexucabtagene autoleucel; del of *TP53*/17p, *TP53* deletion or 17p deletion; NRM, non-relapse mortality; OS, overall survival; R/R MCL, relapsed/refractory mantle cell lymphoma.

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- Full author disclosures are available through the virtual meeting platform

This study is a collaboration between CIBMTR and Kite, a Gilead Company. CIBMTR® is a research collaboration between National Marrow Donor Program® and the Medical College of Wisconsin

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