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Efficacy and safety of bridging therapy prior to CAR T-cell therapy in relapsed or refractory multiple myeloma

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Abstract

Disease burden at the time of BCMA-directed chimeric antigen receptor (CAR) T-cell infusion is a key determinant of outcome in relapsed or refractory multiple myeloma (RRMM). Bridging therapy is frequently administered between leukapheresis and infusion to prevent disease progression, yet its clinical impact remains unclear. We conducted a multicenter real-world cohort study of 399 patients with RRMM treated with BCMA-directed CAR T-cell therapy, including 348 (87%) who received bridging therapy. Bridging therapy recipients had more advanced and biologically adverse disease, including higher rates of high-risk cytogenetics and penta-class refractoriness. Bridging efficacy varied substantially by regimen ($P<0.001$). Bispecific T-cell engager-based bridging, particularly talquetamab, achieved the deepest responses and most effectively converted refractory disease prior to infusion, including in penta-refractory patients. Depth of response achieved after bridging was strongly associated with post-CAR T-cell progression-free survival, independent of baseline disease status. One-year progression-free survival ranged from 87% with talquetamab bridging to 52% with chemotherapy-based approaches. Bridging therapy did not impair subsequent CAR T-cell efficacy and was not associated with excess severe cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, or non-relapse mortality, although infection risk varied across regimens and was associated with pre-lymphodepletion immunoglobulin levels. In summary, these data demonstrate that bridging therapy is not a uniform intervention but a biologically and clinically consequential component of the CAR T-cell treatment pathway. Selection of highly active, immune-compatible bridging regimens can meaningfully improve pre-infusion disease control and post-infusion outcomes without compromising safety.

Introduction

Disease burden at the time of BCMA-directed chimeric antigen receptor (CAR) T-cell infusion has emerged as a key determinant of clinical outcome in relapsed or refractory multiple myeloma (RRMM).[1,2] Multiple studies have demonstrated that lower tumor burden at infusion is associated with higher response rates, prolonged progression-free survival (PFS), and a reduced incidence of severe CAR T-related toxicities.[3–5] Accordingly, achieving disease control before CAR T-cell infusion has become a clinically meaningful objective in patients proceeding to CAR T-cell therapy.[6,7]

Despite these considerations, the clinical impact of bridging therapy remains incompletely defined. During the interval between apheresis and infusion, bridging therapy is administered in a substantial proportion of patients in routine practice to prevent disease progression and clinical deterioration.[4,6,8] This period represents a critical window, in which disease burden, T-cell fitness, and treatment-related inflammatory toxicity jointly influence subsequent outcomes of CAR-T cell therapy.[9] Real-world retrospective studies have yielded inconsistent evidence on the advantage of bridging therapy,[10–13] with some suggesting benefit in disease control, while others raise concerns that intervening therapy during manufacturing may impaired immune recovery or increase downstream toxicity.

The recent introduction of bispecific antibodies has further expanded the bridging landscape, providing potent off-the-shelf T-cell-redirecting therapies capable of achieving rapid disease control.[14,15] While their role in treatment sequencing continues to evolve, early experiences suggest promising activity when used during the manufacturing window,[13] although their impact on subsequent CAR T-cell efficacy and toxicity remains uncertain.[16]

Collectively, these observations underscore the unresolved balance between disease stabilization, immune perturbation, and treatment-related risk inherent to bridging strategies. More broadly, the increasing heterogeneity of bridging regimens highlights the absence of a robust evidence base to guide regimen selection in clinical practice. To address this gap, we conducted a comprehensive real-world analysis of patients treated with BCMA-directed CAR T-cell therapy, stratified by bridging regimen, to clarify the clinical consequences of bridging therapy choice on efficacy, toxicity and survival outcomes.

Methods

Study Design and Patient Cohort

We conducted a retrospective cohort study of consecutive adult patients with relapsed or refractory multiple myeloma who received BCMA-directed CAR T-cell therapy at participating centers (listed in Supplementary Table S1). The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the institutional review boards or ethics committees of all participating centers. Written informed consent was obtained from all patients. Patients were included if they underwent leukapheresis and proceeded to CAR T-cell infusion until the end of 2024 with a commercially available or academic BCMA-directed CAR T-cell product; patients enrolled in prospective clinical trials were excluded. Patients who did not receive CAR T-cell infusion after leukapheresis were also excluded from this analysis. Patients were stratified according to receipt of bridging therapy administered between leukapheresis and CAR T-cell infusion. Bridging therapy was defined as any anti-myeloma treatment delivered after leukapheresis and prior to lymphodepleting chemotherapy, irrespective of intent, regimen, or duration. Patients who received no systemic anti-myeloma therapy during this interval were classified as the no-bridging

group. Supportive care measures alone, including short-course corticosteroids administered for symptom control without anti-myeloma intent, were not considered bridging therapy.

Baseline demographic, disease-related, and treatment-related characteristics were collected prior to bridging therapy if applicable and at the time of CAR T-cell infusion. Disease response,[17] and presence of extramedullary disease (EMD)[18] were defined in accordance with current consensus. High-risk disease was defined according to the International Myeloma Society/International Myeloma Working Group consensus recommendations[19]. Penta-class refractoriness was defined as resistant to at least two immunomodulatory drugs (IMiD), i.e., lenalidomide and pomalidomide; two different proteasome inhibitors, i.e., bortezomib, ixazomib and/or carfilzomib; and one of the CD38 monoclonal antibodies, i.e., daratumumab or isatuximab.

Bridging regimens were categorized based on dominant mechanism of action into prespecified groups for analysis, including IMiD-based therapy, anti-CD38 monoclonal antibody-based therapy, cytotoxic chemotherapy (including combination chemotherapy, single agent cyclophosphamide or bendamustine), bispecific antibody-based therapy with either talquetamab or teclistamab, targeted therapy (including investigational BRAF inhibition and venetoclax-based regimens), and local therapy (radiotherapy). Patients receiving combination regimens were classified according to the principal systemic agent, as determined by treating physician intent and regimen composition.

Outcomes

To minimize immortal time bias, clinical outcomes were assessed from the time of apheresis. Main endpoints included overall response rate after bridging therapy and

before CAR T-cell infusion and progression-free survival after CAR T-cell infusion. Secondary endpoints included CAR T-cell-related toxicities including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), and non-relapse mortality. Safety events were graded using standard criteria in effect at the time of treatment.[20]

Statistical Analysis

Baseline characteristics were summarized using descriptive statistics. Continuous variables were reported as medians with ranges and compared using the Wilcoxon rank-sum test. Categorical variables were summarized as counts and percentages and compared using the χ^2 test or Fisher's exact test, as appropriate. Missing data were reported explicitly and not imputed. Time-to-event outcomes were estimated using the Kaplan-Meier method and compared between groups using the log-rank test. Patients were censored at last follow-up if no event had occurred. Logistic regression with data density modeling and cubic splines were used for analysis of relationships between continuous variables and outcome. Multivariable analysis of progression-free survival was performed using Cox proportional hazards regression. Given the time-dependent and non-randomized nature of bridging therapy administration, baseline imbalances, limited subgroup sizes, and substantial heterogeneity of bridging regimens, multivariable analyses of individual bridging regimens were not performed and comparisons within the bridged cohort were considered strictly exploratory and descriptive.[21,22] Confidence interval widths have not been adjusted for multiplicity and may not be used in place of hypothesis testing. All statistical tests were two-sided (P-value <0.05 was considered statistically significant), and analyses were performed with R statistical software version 4.3.3.

Results

Patients

The study cohort comprised 399 patients treated with BCMA-directed CAR T-cell therapy, of whom 348 patients (87%) received bridging therapy and 51 (13%) did not (Table 1). Baseline demographic characteristics were well balanced between the two groups, including comparable median age (64 versus 63 years, P=0.19), ECOG performance status, and prior autologous or allogeneic transplantation (Table 1, Supplementary Table S2). As expected, differences emerged in disease and treatment characteristics between the bridging and non-bridging group. Patients receiving bridging therapy had a higher prevalence of high-risk cytogenetic abnormalities (37% versus 20%, P=0.02), had been exposed to more prior lines of therapy (median 6 versus 5, P=0.05) and were more frequently penta-class refractory (27% versus 12%, P=0.02). Notably, a higher proportion of patients in the bridging cohort received cilta-cel (P=0.02) and experienced a longer interval between apheresis and CAR T-cell infusion (median of 63 days versus 52 days; P=0.002).

Bridging regimen efficacy

The distribution of bridging regimens demonstrated substantial heterogeneity (Figure 1A), with IMiD-based therapies constituting the most frequently employed approach (20%). Among antibody-based therapies, isatuximab was used in 14% of cases, followed by elotuzumab and daratumumab (12% each). In terms of bispecific T-cell engagers, talquetamab was used in 14% and teclistamab in 3% of cases. Conventional chemotherapy combinations accounted for a smaller proportion of bridging strategies (6%). Targeted therapy (predominantly venetoclax-based regimens, with a minority of patients receiving investigational BRAF inhibition) accounted for 5% of patients.

Disease status before bridging differed significantly (P=0.02) across regimens. Most regimen groups included 75% to 100% of patients in less than partial remission (PR), while patients treated with daratumumab-based or targeted regimen were more likely to be in at least PR at treatment initiation (41% and 50%, respectively). Across regimens, one-fifth to one-third of patients across regimens had penta-refractory disease, with the highest proportion observed among those treated with conventional chemotherapy (33%), followed by teclistamab (30%, 3/10), IMiDs (27%), daratumumab (22%), talquetamab (20%), isatuximab (20%), and elotuzumab (19%).

Overall response to bridging differed substantially by regimen (P<0.001; Figure 1B). Among bispecific T-cell engagers, talquetamab demonstrated the greatest depth of response, with a low rate of <PR (14%) and high frequencies of very good PR (VGPR, 41%) and ≥CR (25%). Teclistamab demonstrated attenuated activity, achieving VGPR in 30% (3/10) of patients with a relatively modest <PR rate (40%). Among monoclonal antibodies, daratumumab showed a more favorable response profile, with VGPR or better in 32% of patients, whereas elotuzumab and isatuximab were characterized by high rates of <PR (72% and 63%, respectively). IMiD-based therapy yielded limited efficacy, with only 10% of patients attaining ≥CR. Similarly, selinexor combinations, single agent cyclophosphamide, bendamustine, and belantamab mafodotin were characterized by poor efficacy, with <PR rates ranging from 63% to 80%. Local radiotherapy resulted exclusively in PR or less, without any CR.

We next investigated the potential impact of refractory status on bridging efficacy (Figure 1B). Penta-refractory disease was associated with a significant lower likelihood of response after bridging compared with non-penta-refractory disease (37% vs 60%; P=0.001). Importantly, in penta-refractory patients, the highest overall response rates were observed with talquetamab (90%) and investigational targeted therapies (60%),

while response rates with other regimens ranged from 16% to 33%. In non-penta-refractory disease, responses were highest with talquetamab (85%), teclistamab (70%, 7/10), daratumumab-based regimen (69%) and investigational targeted therapies (67%). We further assessed the capacity of each bridging regimen to convert pre-bridging disease status to response prior to CAR T-cell infusion and found significant differences (P<0.001; Figure 1C). Among patients with <PR before bridging, overall response rates were highest with talquetamab (81%) and teclistamab bridging therapy (60%, 6/10), and lowest with elotuzumab- (6%) and isatuximab-based bridging (18%). The responses with other regimens ranged from 25% to 33%.

After bridging, CAR T-cell therapy further deepened or converted responses in a product-dependent manner (Figure 1D). Overall response rates among evaluable patients were 83% for ide-cel, 97% for cilta-cel, and 100% for academic CAR T-cell therapy (P<0.001). In addition, cilta-cel and academic CAR T-cell therapy were much more likely to convert refractory disease after bridging into response, including CR.

After a median follow-up of 14 months (95% confidence interval, 13 to 15 months) for the total cohort, 1-year progression-free survival (PFS) differed across bridging regimen (Figure 2A), with rates of 87% for talquetamab, 81% for daratumumab, 81% for targeted therapy, 73% for teclistamab, 73% for isatuximab, 67% for IMiD, 64% for elotuzumab, and 52% for chemotherapy. Response status after bridging and prior to CAR T-cell infusion was strongly associated with outcome (P<0.001; Figure 2B). The 1-year PFS was 85% for ≥CR, 88% for VGPR, 73% for PR, and 53% for <PR. A similar pattern was observed among patients with <PR before bridging, with a 1-year PFS estimate of 92% for those achieving ≥CR, 91% for VGPR, 69% for PR, and 53% for <PR (Supplemental Figure 1A).

Bridging regimen safety

We next investigated bridging-specific and CAR T-cell-specific toxicities. Hematologic recovery after bridging and before lymphodepletion for CAR T-cell therapy was generally comparable across regimens with respect to neutrophil and platelet counts (Figure 3A). In contrast, post-bridging hemoglobin levels differed significantly between regimens (P=0.045). The incidence of CRS after CAR T-cell infusion differed by bridging regimen (P=0.01; Figure 3B), occurring in approximately 80-90% of patients across most regimens, predominantly as grade 1-2. Of note, CRS incidence was lowest in patients receiving bispecific T-cell engager-based bridging, being at 69% with talquetamab and 50% (5/10) for teclistamab. The incidence of ICANS was generally comparable between bridging regimens (P=0.35), with most rates ranging from 10% to 19%. Two regimens demonstrated higher ICANS incidence (>20%): elotuzumab (21%), and investigational targeted therapy (25%, all of whom received venetoclax-containing bridging: two grade 1, one grade 3, and one grade 4). Furthermore, patients achieving deep disease control with bridging therapy (≥VGPR) had lower rates of CRS than those with ≤PR at lymphodepletion (any-grade 70% vs 87%, RR 1.24, 95% CI 1.07-1.45; grade ≥2 19.5% vs 33.7%, RR 1.73, 95% CI 1.07-2.81), with a concordant but non-significant trend for ICANS (11% vs 14%). Delayed neurotoxicity did not differ by bridging regimen (P=0.29) and was primarily driven by CAR T-cell product (11% for cilta-cel and 4% for ide-cel). Infections of any grade occurred in 43% of patients following CAR T-cell infusion, ranging from 28% to 61% across bridging regimens (P=0.02; Figure 3C). IgG levels prior to lymphodepletion were not affected by bridging regimen (P=0.53), but were associated with the incidence of infections post-CAR T-cell infusion (P<0.001; Figure 3D), following a U-shaped relationship, with low and high levels of IgG being associated with increased risk for infection.

Bridging versus no bridging

Lastly, we performed exploratory analyses comparing patients who received bridging therapy with those who did not. One-year estimates for PFS and overall survival (OS) were 70% (95% confidence interval, 64 to 75%) and 86% (95% confidence interval, 82 to 90%) in the bridging group versus 79% (95% confidence interval, 67 to 91%) and 88% (95% confidence interval, 78-97%) in the non-bridging group, respectively (Supplemental Figure S2A&B). To address baseline imbalances between bridged and non-bridged patients, we fitted a multivariable Cox model for PFS with the time origin set at lymphodepletion, so that bridging and all covariates were fully ascertained before follow-up began and immortal-time bias did not arise. After adjustment for age, ECOG, extramedullary disease, high-risk cytogenetics, disease status, and penta-refractoriness, bridging was not independently associated with PFS (HR 1.30, 95% CI 0.78-2.24), a result unchanged when the time origin was set at apheresis (HR 1.28, 95% CI 0.74-2.20) or when penta-refractoriness - the only covariate with non-proportional hazards - was handled by stratification (HR 1.16, 95% CI 0.68-1.99; Supplemental Figure S2C).

Regarding CAR T-cell specific toxicities, patients receiving bridging experienced higher rates of CRS of any grade (83%) versus those without bridging (72%), largely driven by grade 1 events (53% versus 37%), while rates of severe CRS grade >2 appeared numerically lower in the bridging-group (2% versus 8%). The incidence of ICANS was comparable between both groups (13% versus 14%). Infection occurred in 43% receiving bridging therapy versus 24% without bridging (unadjusted RR 1.82, 95% CI 1.09-3.03; p=0.009). 1-year non-relapse mortality was 4% (95% confidence interval, 2 to 6%) with bridging versus 2% (95% confidence interval, 0 to 6%) without bridging.

Discussion

In this large multi-center international study, we demonstrate that response to bridging therapy is a key determinant of outcomes following BCMA-directed CAR T-cell therapy. These findings add important context to the ongoing debate regarding the clinical value of bridging therapy beyond maintaining clinical stability and eligibility for CAR T-cell infusion. Notably, our data indicate that talquetamab represents a particularly effective bridging option, achieving high response rates even in penta-refractory disease, associating with improved post-CAR T-cell outcomes, and exhibiting a more favorable toxicity profile during subsequent CAR T-cell therapy.

Whether bridging therapy can provide meaningful benefit beyond disease control during the manufacturing interval has remained a subject of debate. Inferior CAR T-cell outcomes have consistently been observed in patients with high tumor burden, including those with extramedullary disease, elevated soluble BCMA levels, or increased metabolic tumor volume.[23,3,7] These associations are likely driven by a combination of tumor-mediated immunosuppression, systemic inflammation resulting in T-cell exhaustion, and an unfavorable effector-to-target ratio.[24,25] Within this framework, effective cytoreduction prior to CAR T-cell infusion represents a biologically plausible strategy to improve CAR T-cell efficacy.

Accordingly, our study demonstrates that achievement of response to bridging therapy is associated with improved CAR T-cell response rates and progression-free survival. These findings are consistent with subgroup analyses from the pivotal phase III trials CARTITUDE-4 and KarMMa-3, which evaluated the currently available BCMA-directed CAR T-cell products and similarly demonstrated an association between response to bridging therapy and superior CAR T-cell outcomes. Notably, this association has not been consistently reproduced in retrospective analyses,[26] likely reflecting limited

cohort sizes and the use of bridging regimens that induced meaningful responses in only a minority of patients.[6,27] Evidence guiding the optimal selection of bridging regimens remains limited, and clinical practice is therefore largely informed by prior treatment exposure rather than comparative prospective data.[28] In this context, it is noteworthy that the KarMMa-3 and CARTITUDE-4 trials restricted bridging therapy to a limited set of regimens, and did not incorporate bispecific antibodies or other agents as bridging approaches.[29,30]

Reflecting the absence of evidence-based guidance, our real-world analysis demonstrates substantial heterogeneity in bridging therapy selection, with marked differences in response rates across regimens. Chemotherapy-, IMiD-, and elotuzumab-based regimens were associated with substantially lower bridging efficacy in our cohort, suggesting limited clinical utility of these approaches in the bridging setting. In contrast, and consistent with prior reports,[6,13] talquetamab bridging achieved high response rates and a greater depth of response, representing the most effective bridging strategy in our cohort.

The optimal sequencing of T-cell-based therapies in multiple myeloma remains incompletely defined. Retrospective analyses have suggested inferior CAR T-cell outcomes in patients previously exposed to bispecific antibodies. While this may primarily reflect a particularly difficult-to-treat patient population and thus introduce selection bias, there is also evidence that bispecific antibody-induced T-cell exhaustion may increase rates of out-of-specification CAR T-cell manufacturing and consequently impair efficacy.[6] In light of these concerns, the European Myeloma Network currently recommends avoiding administration of bispecific antibodies in close temporal proximity to leukapheresis.[28] Additional caution specifically applies to BCMA-directed bispecific T-cell engagers, as BCMA antigen loss represents a common resistance mechanism that may further impair the efficacy of subsequent BCMA-directed CAR T-

cell therapy.[28,31]

Against this background, our study highlights the potential utility of bispecific antibodies - particularly talquetamab - when applied in a carefully defined bridging context prior to CAR T-cell therapy. Only recently have bispecific antibodies emerged as a feasible option for bridging before CAR T-cell infusion.[13] While earlier reports from small patient cohorts demonstrated that bispecific antibody-based bridging could induce deeper remissions prior to CAR T-cell therapy compared with other regimens, these responses did not consistently translate into superior CAR T-cell outcomes. In contrast, our real-world data show that talquetamab bridging was associated not only with high response rates and greater depth of remission prior to infusion, but also with improved CAR T-cell response rates and progression-free survival. Differences between our findings and prior reports may primarily reflect limited patient numbers in earlier cohorts.[26]

The impact of bridging therapy on the safety of subsequent CAR T-cell treatment remains an important consideration, and several studies have emphasized the need to carefully balance potential benefit against harm. Prior analyses have raised concerns that bridging therapy may increase the risk of both CAR T-cell-related and non-CAR T-cell-related toxicities. In our cohort, rates of CRS were higher in bridged patients compared with non-bridged patients; however, this observation is likely influenced by baseline differences and confounding by indication. Patients requiring bridging therapy constitute a biologically and clinically distinct population, characterized by more advanced and refractory disease, including a higher prevalence of high-risk cytogenetic abnormalities, greater prior treatment exposure, and higher rates of penta-class refractoriness. These adverse baseline features are established to correlate with an increased risk of CAR T-cell-associated toxicities.[32,33] Notably, CRS rates were significantly lower among patients receiving bispecific T-cell engager-based bridging compared to other bridging regimens, a finding that is consistent with previous reports.[6]

Hematologic toxicity and recovery after CAR T-cell therapy represent another increasingly recognized aspect of treatment safety. Intensive chemotherapy-based bridging regimens have previously been associated with delayed hematologic recovery following CAR T-cell therapy and with the occurrence of immune effector cell-associated hematotoxicity.[11,12] In our analysis, neutrophil and platelet recovery after bridging therapy appeared largely comparable across regimens, whereas greater heterogeneity was observed in hemoglobin levels, suggesting differential effects of bridging strategies on erythropoietic recovery. However, definitive conclusions regarding the impact of bridging therapy on the occurrence of hematotoxicity are limited by the lack of serial hematologic assessments following CAR T-cell infusion in this study.

This study has several limitations. First, its retrospective, non-randomized design precludes causal inference and is inherently susceptible to confounding by indication and selection bias, particularly given the close relationship between bridging regimen selection and underlying disease severity, refractoriness, and prior treatment exposure. Multivariable analyses were performed where feasible to account for baseline imbalances between bridged and non-bridged patients. However, adjusted comparisons between individual bridging therapy regimens were not undertaken because the substantial heterogeneity of bridging strategies and the resulting limited subgroup sizes restricted the feasibility of robust adjusted analyses. Consequently, all between-group comparisons are presented as strictly exploratory and descriptive, and confidence intervals should be interpreted without inferring confirmatory hypothesis testing. Second, bridging therapy selection was not standardized but guided by treating physician judgment, reflecting real-world practice while limiting direct inter-regimen comparability. Third, the absence of serial hematologic and immune monitoring following CAR T-cell infusion limits definitive assessment of bridging-related

hematotoxicity and immune reconstitution. These limitations underscore the hypothesis-generating nature of our findings and reinforce the need for prospective studies to establish evidence-based bridging strategies.

In summary, our findings indicate that response to bridging therapy is associated with improved outcomes following BCMA-directed CAR T-cell therapy, suggesting that bridging therapy should be considered not merely as a stabilizing measure, but as a clinically relevant component of the CAR T-cell treatment pathway. Within the limitations of this retrospective analysis, talquetamab-based bridging demonstrated favorable efficacy across disease subgroups, including penta-refractory disease, and was associated with a lower incidence of CRS compared with other regimens. These observations support the rationale for prospective evaluation of optimized bridging strategies - including the role of non-BCMA-directed bispecific antibodies - to refine the sequencing of T-cell-based therapies in RRMM.

References

1. Munshi NC, Anderson LD Jr, Shah N, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. N Engl J Med. 2021;384(8):705-716.

2. Jagannath S, Martin TG, Lin Y, et al. Long-Term (≥5-Year) Remission and Survival After Treatment With Ciltacabtagene Autoleucel in CARTITUDE-1 Patients With Relapsed/Refractory Multiple Myeloma. J Clin Oncol. 2025;43(25):2766-2771.

3. Sidana S, Patel KK, Peres LC, et al. Safety and efficacy of standard-of-care ciltacabtagene autoleucel for relapsed/refractory multiple myeloma. Blood. 2025;145(1):85-97.

4. Merz M, Gagelmann N, Smaili S, et al. Remission conversion drives outcomes after CAR T-cell therapy for multiple myeloma: a registry analysis from the DRST. Blood. 2025;146(14):1677-1686.

5. Zabaleta A, Puig N, Cedena MT, et al. Clinical significance of complete remission and measurable residual disease in relapsed/refractory multiple myeloma patients treated with T-cell redirecting immunotherapy. Am J Hematol. 2025;100(1):93-102.

6. Fandrei D, Seiffert S, Rade M, et al. Bispecific antibodies as bridging to BCMA CAR-T cell therapy for relapsed/refractory multiple myeloma. Blood Cancer Discov. 2025;6(1):38-54.

7. Gagelmann N, Dima D, Merz M, et al. Development and validation of a prediction model of outcome After B-Cell maturation antigen-directed chimeric antigen receptor T-Cell therapy in relapsed/refractory multiple myeloma. J Clin Oncol. 2024;42(14):1665-1675.

8. Richter J. Like a bridge over troubled water: keeping the myeloma down en route to CAR-T. Blood Cancer J. 2024;14(1):64.

9. Rade M, Fandrei D, Kreuz M, et al. A longitudinal single-cell atlas to predict outcome and toxicity after BCMA-directed CAR T cell therapy in multiple myeloma. Cancer Cell. 2026;44(3):586-6203.e9.

10. Manjunath SH, Cohen AD, Lacey SF, et al. The safety of bridging radiation with anti-BCMA CAR T-cell therapy for multiple myeloma. Clin Cancer Res. 2021;27(23):6580-6590.

11. Frenking JH, Zhou X, Rejeski K, et al. Bridging intensity is associated with impaired hematopoietic recovery after BCMA CAR-T therapy for multiple myeloma. Blood Adv. 2025;9(16):4151-4166.

12. Zafar A, Huang CY, Lo M, et al. Intensity of cyclophosphamide-based bridging therapy before chimeric antigen receptor T cell therapy in myeloma. Transplant Cell Ther. 2023;29(8):504.e1-e504.e7.

13. Dhakal B, Akhtar OS, Fandrei D, et al. Sequential targeting in multiple myeloma: talquetamab, a GPRC5D bispecific antibody, as a bridge to BCMA CAR-T therapy. Blood. 2025;146(17):2063-2072.

14. Chari A, Minnema MC, Berdeja JG, et al. Talquetamab, a T-cell-redirecting GPRC5D bispecific antibody for multiple myeloma. N Engl J Med. 2022;387(24):2232-2244.

15. Moreau P, Garfall AL, van de Donk NWCJ, et al. Teclistamab in relapsed or refractory multiple myeloma. N Engl J Med. 2022;387(6):495-505.

16. Jelinek T, Žihala D, Zabaleta A, et al. Selective depletion of B-cell subsets underlies increased risk of infection in MM patients treated with anti-BCMA vs -GPRC5D bsAbs. Blood. 2026;147(10):1070-1082.

17. Lin Y, Qiu L, Usmani S, et al. Consensus guidelines and recommendations for the management and response assessment of chimeric antigen receptor T-cell therapy in clinical practice for relapsed and refractory multiple myeloma: a report from the International Myeloma Working Group Immunotherapy Committee. Lancet Oncol. 2024;25(8):e374-e387.

18. Rosiñol L, Beksac M, Zamagni E, et al. Expert review on soft-tissue plasmacytomas in multiple myeloma: definition, disease assessment and treatment considerations. Br J Haematol. 2021;194(3):496-507.

19. Avet-Loiseau H, Davies FE, Samur MK, et al. International Myeloma Society/International Myeloma Working Group consensus recommendations on the definition of high-risk multiple myeloma. J Clin Oncol. 2025;43(24):2739-2751.

20. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019;25(4):625-638.

21. Brookhart MA, Stürmer T, Glynn RJ, Rassen J, Schneeweiss S. Confounding control in healthcare database research: challenges and potential approaches. Med Care. 2010;48(6 Suppl):S114-S120.

22. Petersen ML, Porter KE, Gruber S, Wang Y, van der Laan MJ. Diagnosing and responding to violations in the positivity assumption. Stat Methods Med Res. 2012;21(1):31-54.

23. Freeman CL, Noble J, Menges M, et al. Tumor burden quantified by soluble B-cell maturation antigen and metabolic tumor volume determines myeloma CAR-T outcomes. Blood. 2025;145(15):1645-1657.

24. Ventin M, Cattaneo G, Maggs L, Arya S, Wang X, Ferrone CR. Implications of high tumor burden on chimeric antigen receptor T-Cell immunotherapy: A Review. JAMA Oncol. 2024;10(1):115-121.

25. Jain MD, Zhao H, Wang X, et al. Tumor interferon signaling and suppressive myeloid cells are associated with CAR T-cell failure in large B-cell lymphoma. Blood. 2021;137(19):2621-2633.

26. Hansen D, Reid B, Grajales-Cruz A, et al. Bridging therapy response and low pre-lymphodepletion plasma cell burden are associated with improved safety and efficacy outcomes of ciltacabtagene autoleucel in multiple myeloma. Blood. 2025;146(Supplement 1):2214.

27. Afrough A, Hashmi H, Hansen DK, et al. Real-world impact of bridging therapy on outcomes of ide-cel for myeloma in the U.S. Myeloma Immunotherapy Consortium. Blood Cancer J. 2024;14(1):63.

28. van de Donk NWCJ, Moreau P, San-Miguel JF, et al. Optimising T-cell immunotherapy in patients with multiple myeloma: practical considerations from the European Myeloma Network. Lancet Haematol. 2025;12(8):e635-e649.

29. Rodriguez-Otero P, Ailawadhi S, Arnulf B, et al. Ide-cel or standard regimens in relapsed and refractory multiple myeloma. N Engl J Med. 2023;388(11):1002-1014.

30. San-Miguel J, Dhakal B, Yong K, et al. Cilta-cel or standard care in lenalidomide-refractory multiple myeloma. N Engl J Med. 2023;389(4):335-347.

31. Firestone RS, Socci ND, Shekarkhand T, et al. Antigen escape as a shared mechanism of resistance to BCMA-directed therapies in multiple myeloma. Blood. 2024;144(4):402-407.

32. Yan Z, Zhang H, Cao J, et al. Characteristics and risk factors of cytokine release syndrome in chimeric antigen receptor t cell treatment. Front Immunol. 2021;12:611366.

33. Pereira R, Bergantim R. An assessment of the effectiveness and safety of chimeric antigen receptor t-cell therapy in multiple myeloma patients with relapsed or refractory disease: a systematic review and meta-analysis. Int J Mol Sci. 2024;25(9):4996.

Table 1. Patient characteristics.

	No bridging (n=51)	Bridging (n=348)	*P*
Age, median (range)	64 (28-84)	63 (37-77)	0.19
Sex, no.(%)			0.88
Male	31 (61)	215 (62)	
Female	20 (39)	133 (38)	
ECOG, no. (%)			
0	26 (52)	158 (46)	
1	18 (36)	165 (48)	
2	5 (10)	16 (5)	
3	1 (2)	4 (1)	
Unknown	1	5	
Extramedullary disease, no. (%)			0.86
Yes	13 (26)	85 (24)	
No	38 (74)	263 (76)	
High-risk cytogenetics, no. (%)			0.02
Yes	8 (20)	114 (37)	
No	33 (80)	191 (63)	
Unknown	10	43	
Prior transplantation, no. (%)			
Autologous	45 (88)	299 (86)	0.83
Allogeneic	4 (8)	24 (7)	0.77
Prior lines of therapy, median (range)	5 (2-9)	6 (2-14)	0.05
Penta-class refractory, no. (%)	6 (12)	93 (27)	0.02
Disease status before bridging or before lymphodepletion if no bridging, no. (%)			0.04
<PR	34 (67)	267 (77)	
PR	6 (12)	51 (15)	
VGPR	9 (18)	26 (8)	
CR	2 (4)	4 (1)	
Time between diagnosis and infusion in years, median (range)	5.7 (0.2-21.6)	6.6 (0.2-29.0)	0.81
Time between apheresis and infusion in days, median (range)	52 (23-128)	63 (22-196)	0.002
CAR-T product, no. (%)			0.02
Cilta-cel	12 (23)	150 (43)	
Ide-cel	32 (63)	170 (49)	
Academic CAR	7 (14)	28 (8)	

Figure legends

Figure 1. Bridging regimen, response rates, and patient flow.

(A) Bridging regimen frequency.

(B) Overall response to bridging in total cohort and in penta-refractory disease. Bridging regimens administered in fewer than 3% of patients were grouped into the category ‘other’.

(C) Alluvial plot of patient flow according to disease status before bridging, bridging regimen, and response to bridging (before CAR T-cell therapy).

(D) Alluvial plot of patient flow according to bridging regimen, response to bridging, subsequent CAR T-cell therapy and product, and overall response after CAR T-cell therapy.

Figure 2. Efficacy by bridging regimen and response.

(A) Progression-free survival according to bridging regimen.

(B) Progression-free survival by overall response status after bridging therapy.

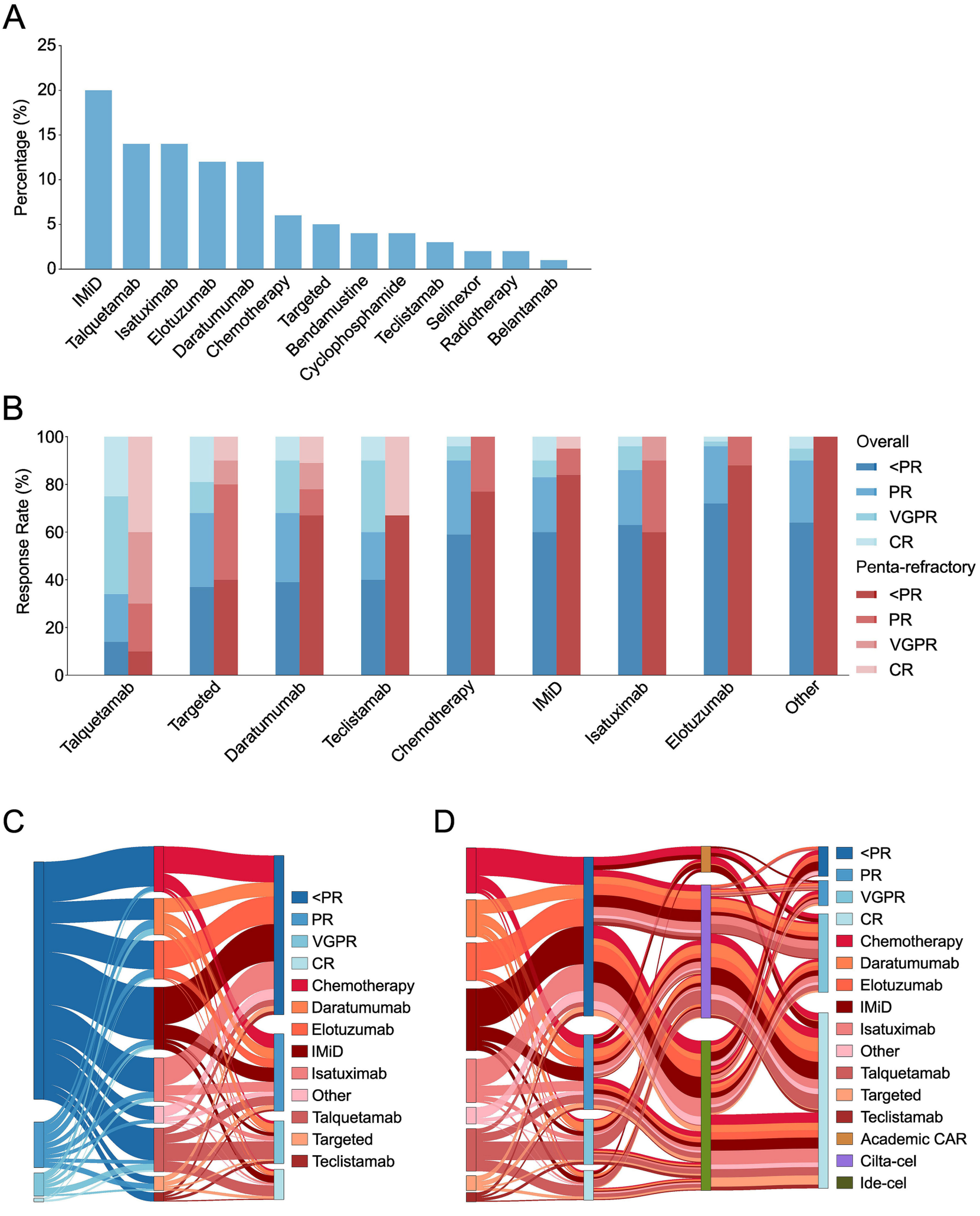
Figure 3. Safety of bridging therapy regimens.

(A) Blood counts after bridging therapy and before start of lymphodepletion, according to bridging regimen. Bridging regimens administered in fewer than 3% of patients were grouped into the category ‘other’.

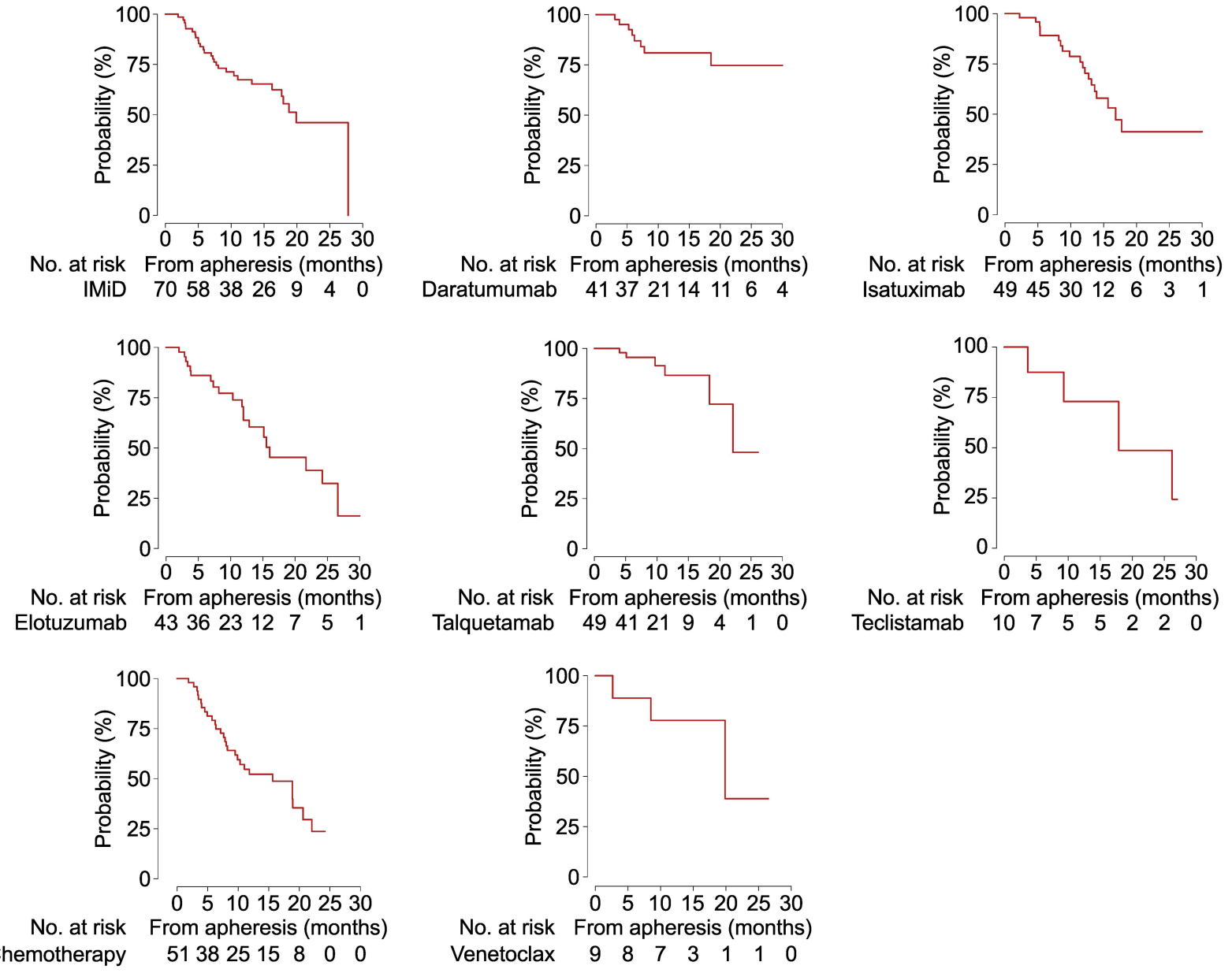
(B) CAR T-specific toxicity with CRS and ICANS, according to bridging regimen. Bridging regimens administered in fewer than 3% of patients were grouped into the category ‘other’.

(C) Infections of any grade after CAR T-cell therapy, according to bridging regimen received. Bridging regimens administered in fewer than 3% of patients were grouped into the category ‘other’.

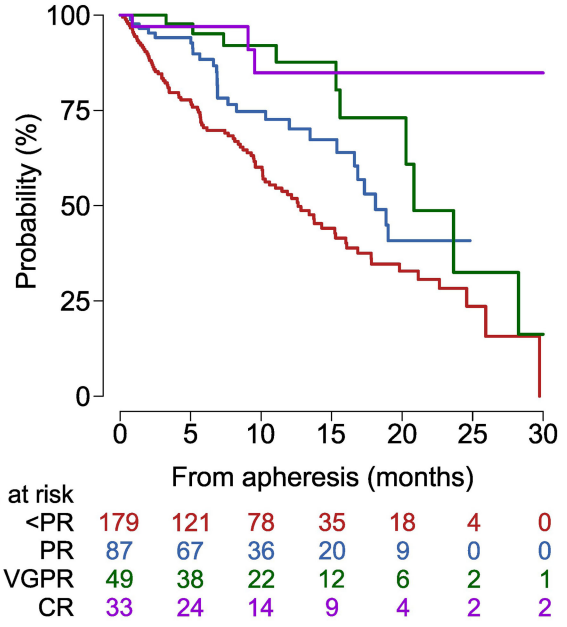
(D) Association of IgG levels after bridging and before lymphodepletion and infection risk after CAR T-cell therapy.

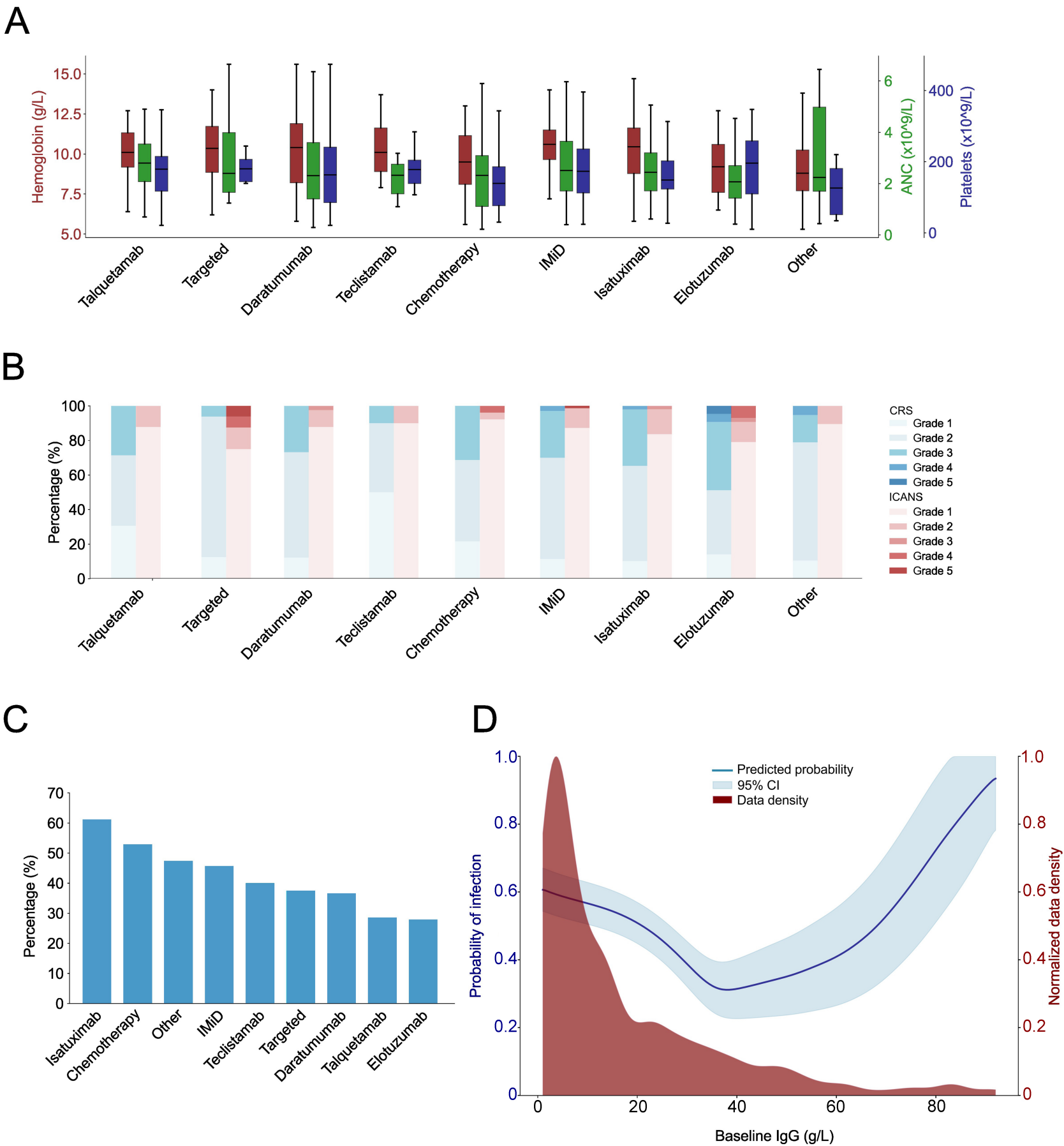

A
Percentage (%)
25
20
15
10
5
0
IMiD
Talquetamab
Isatuximab
Elotuzumab
Daratumumab
Chemotherapy
Targeted
Bendamustine
Cyclophosphamide
Teclistamab
Selinexor
Radiotherapy
Belantamab
B
Response Rate (%)
100
80
60
40
20
0
Talquetamab
Targeted
Daratumumab
Teclistamab
Chemotherapy
IMiD
Isatuximab
Elotuzumab
Other
Overall
<PR
PR
VGPR
CR
Penta-refractory
<PR
PR
VGPR
CR
C
<PR
PR
VGPR
CR
Chemotherapy
Daratumumab
Elotuzumab
IMiD
Isatuximab
Other
Talquetamab
Targeted
Teclistamab
D
<PR
PR
VGPR
CR
Chemotherapy
Daratumumab
Elotuzumab
IMiD
Isatuximab
Other
Talquetamab
Targeted
Teclistamab
Academic CAR
Cilta-cel
Ide-cel

A


Probability (%)
100
75
50
25
0
0 5 10 15 20 25 30
No. at risk From apheresis (months)
IMiD 70 58 38 26 9 4 0
Daratumumab 41 37 21 14 11 6 4
Isatuximab 49 45 30 12 6 3 1
Elotuzumab 43 36 23 12 7 5 1
Talquetamab 49 41 21 9 4 1 0
Teclistamab 10 7 5 5 2 2 0
Chemotherapy 51 38 25 15 8 0 0
Venetoclax 9 8 7 3 1 1 0

B


Probability (%)
100
75
50
25
0
0 5 10 15 20 25 30
From apheresis (months)
No. at risk
<PR 179 121 78 35 18 4 0
PR 87 67 36 20 9 0 0
VGPR 49 38 22 12 6 2 1
CR 33 24 14 9 4 2 2


A
Hemoglobin (g/L)
15.0
12.5
10.0
7.5
5.0
ANC (x10^9/L)
6
4
2
0
Platelets (x10^9/L)
400
200
0
Talquetamab
Targeted
Daratumumab
Teclistamab
Chemotherapy
IMiD
Isatuximab
Elotuzumab
Other
B
Percentage (%)
100
80
60
40
20
0
CRS
Grade 1
Grade 2
Grade 3
Grade 4
Grade 5
ICANS
Grade 1
Grade 2
Grade 3
Grade 4
Grade 5
Talquetamab
Targeted
Daratumumab
Teclistamab
Chemotherapy
IMiD
Isatuximab
Elotuzumab
Other
C
Percentage (%)
70
60
50
40
30
20
10
0
Isatuximab
Chemotherapy
Other
IMiD
Teclistamab
Targeted
Daratumumab
Talquetamab
Elotuzumab
D
Predicted probability
95% CI
Data density
Probability of infection
1.0
0.8
0.6
0.4
0.2
0
Normalized data density
1.0
0.8
0.6
0.4
0.2
0
0
20
40
60
80
Baseline IgG (g/L)

Supplement for:

Response to Bridging Therapy Prior to CAR T-Cell Therapy in Relapsed or Refractory Multiple Myeloma

Wesener et al.

Content

Table S1: Participating centers and corresponding patient numbers.

Center	N
Leipzig	97
Bern	55
Essen	52
Dresden	35
Kiel	35
Barcelona	35
Erlangen	21
Düsseldorf	18
Berlin	17
Bonn	17
Linz	17
Total	399

Table S2. Selected characteristics before bridging.

	IMiD	**Tec**	**Tal**	**Chemo**	**Isa**	**Elo**	**Dara**	**Target**	**Other**
No. of patients	70	10	49	51	49	43	41	16	19
Prior auto	83%	80%	80%	78%	98%	93%	95%	88%	68%
Prior allo	7%	0%	6%	12%	8%	7%	5%	0%	5%
Disease status before bridging									
<PR	84%	100%	74%	88%	78%	75%	59%	50%	79%
PR	9%	0%	8%	10%	14%	21%	24%	38%	21%
VGPR	6%	0%	14%	2%	8%	2%	17%	12%	0%
>VGPR	1%	0%	4%	0%	0%	2%	0%	0%	0%
Extramedullary disease	26%	0%	20%	37%	27%	26%	17%	25%	16%
BCMA exposure before briding	10%	0%	8%	14%	16%	5%	2%	13%	21%

Supplemental Figure legends

Supplemental Figure 1. Bridging therapy response and its association with progression-free survival.

(A) Progression-free survival by response conversion for patients with less than partial response before start of bridging therapy.

Supplemental Figure 2. Progression-free and overall survival after CAR-T by bridging status.

(A) Kaplan-Meier estimates of progression-free survival (PFS) from time of apheresis, stratified by receipt of bridging therapy. Numbers at risk are shown below each panel.

(B) Kaplan-Meier estimates of overall survival (OS) from time of apheresis, stratified by receipt of bridging therapy. Numbers at risk are shown below each panel.

(C) Forest plot showing hazard ratios (HRs) for PFS associated with bridging therapy versus no bridging in multivariable Cox regression analyses. The primary model was adjusted for age, ECOG performance status, extramedullary disease, high-risk cytogenetics, disease status, and penta-refractoriness, with follow-up starting at lymphodepletion. Sensitivity analyses were performed using apheresis as the time origin and by stratifying for penta-refractoriness. Error bars represent 95% confidence intervals.

Figure S1

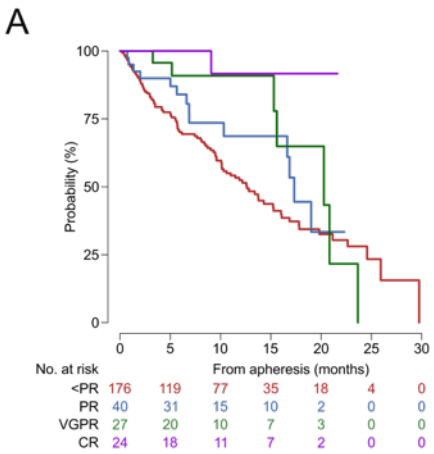
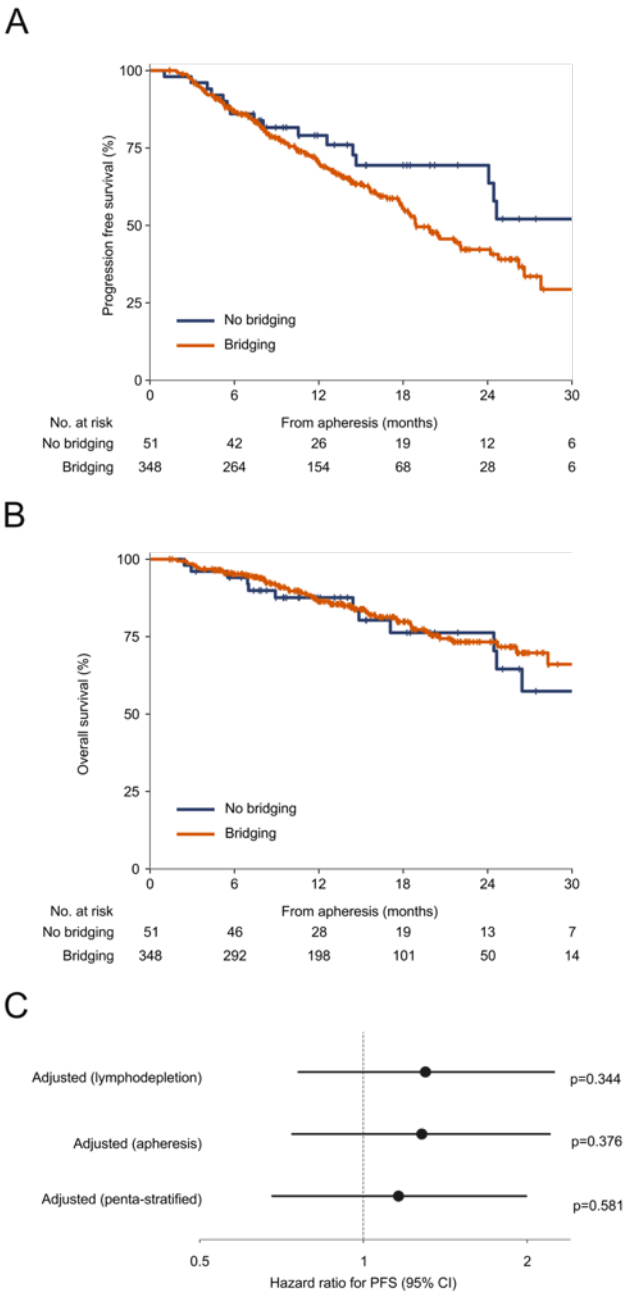

A
100
75
50
25
0
Probability (%)
0
5
10
15
20
25
30
From apheresis (months)
No. at risk
<PR 176 119 77 35 18 4 0
PR 40 31 15 10 2 0 0
VGPR 27 20 10 7 3 0 0
CR 24 18 11 7 2 0 0

Figure S2.


A
Progression free survival (%)
100
75
50
25
0
No bridging
Bridging
0
6
12
18
24
30
From apheresis (months)
No. at risk
No bridging 51 42 26 19 12 6
Bridging 348 264 154 68 28 6
B
Overall survival (%)
100
75
50
25
0
No bridging
Bridging
0
6
12
18
24
30
From apheresis (months)
No. at risk
No bridging 51 46 28 19 13 7
Bridging 348 292 198 101 50 14
C
Adjusted (lymphodepletion)
p=0.344
Adjusted (apheresis)
p=0.376
Adjusted (penta-stratified)
p=0.581
0.5
1
2
Hazard ratio for PFS (95% CI)