haematologica
Journal of the Ferrata Storti Foundation

Characterization and impact of response to holding/bridging therapy in second-line large B-cell lymphoma patients treated with axicabtagene ciloleucel: a LYSA study from the French DESCAR-T registry

by Antoine Capes, Caroline Rossoni, Elodie Gat, Guillaume Cartron, François-Xavier Gros, Emmanuel Bachy, Guillaume Manson, Gabriel Brisou, Catherine Thieblemont, Stéphanie Guidez, Laurianne Drieu La Rochelle, Rémy Dulery, Florent Malard, Fabrice Jardin, Benoît Tessoulin, Fabien Le Bras, Franck Morschhauser, Amandine Durand, Cristina Castilla Llorente, Pierre Bories, Michaël Loschi, Sylvain Choquet, Gandhi-Laurent Damaj, Marie-Thérèse Rubio, Aline Tanguy-Schmidt, Jacques-Olivier Bay, Magalie Joris, Sylvain Carras, Laure Lebras, Julie Abraham, Jean-Valère Malfuson, Ludovic Fouillet, Olivier Hermine, Adrien Chauchet, Laura Herbreteau, Blandine Guffroy, Justine Decroocq, Steven Le Gouill, Roch Houot and Estelle Bourbon

Received: July 6, 2026.
Accepted: November 9, 2026.

Citation: Antoine Capes, Caroline Rossoni, Elodie Gat, Guillaume Cartron, François-Xavier Gros, Emmanuel Bachy, Guillaume Manson, Gabriel Brisou, Catherine Thieblemont, Stéphanie Guidez, Laurianne Drieu La Rochelle, Rémy Dulery, Florent Malard, Fabrice Jardin, Benoît Tessoulin, Fabien Le Bras, Franck Morschhauser, Amandine Durand, Cristina Castilla Llorente, Pierre Bories, Michaël Loschi, Sylvain Choquet, Gandhi-Laurent Damaj, Marie-Thérèse Rubio, Aline Tanguy-Schmidt, Jacques-Olivier Bay, Magalie Joris, Sylvain Carras, Laure Lebras, Julie Abraham, Jean-Valère Malfuson, Ludovic Fouillet, Olivier Hermine, Adrien Chauchet, Laura Herbreteau, Blandine Guffroy, Justine Decroocq, Steven Le Gouill, Roch Houot and Estelle Bourbon. Characterization and impact of response to holding/bridging therapy in second-line large B-cell lymphoma patients treated with axicabtagene ciloleucel: a LYSA study from the French DESCAR-T registry.
Haematologica. 2026 Nov 19. doi: 10.3324/haematol.2026.301559 [Epub ahead of print]

Publisher's Disclaimer.
E-publishing ahead of print is increasingly important for the rapid dissemination of science. Haematologica is, therefore, E-publishing PDF files of an early version of manuscripts that have completed a regular peer review and have been accepted for publication.
E-publishing of this PDF file has been approved by the authors.
After having E-published Ahead of Print, manuscripts will then undergo technical and English editing, typesetting, proof correction and be presented for the authors' final approval, the final version of the manuscript will then appear in a regular issue of the journal.
All legal disclaimers that apply to the journal also pertain to this production process.

Characterization and impact of response to holding/bridging therapy in second-line large B-cell lymphoma patients treated with axicabtagene ciloleucel: a LYSA study from the French DESCAR-T registry

Antoine Capes[1], Caroline Rossoni[2], Elodie Gat[2], Guillaume Cartron[3], François-Xavier Gros[4], Emmanuel Bachy[5], Guillaume Manson[6], Gabriel Brisou[7], Catherine Thieblemont[8], Stéphanie Guidez[9], Laurianne Drieu La Rochelle[10], Rémy Dulery[1], Florent Malard[1], Fabrice Jardin[11], Benoît Tessoulin[12], Fabien Le Bras[13], Franck Morschhauser[14], Amandine Durand[15], Cristina Castilla Llorente[16], Pierre Bories[17], Michaël Loschi[18], Sylvain Choquet[19], Gandhi-Laurent Damaj[20], Marie-Thérèse Rubio[21], Aline Tanguy-Schmidt[22], Jacques-Olivier Bay[23], Magalie Joris[24], Sylvain Carras[25], Laure Lebras[26], Julie Abraham[27], Jean-Valère Malfuson[28], Ludovic Fouillet[29], Olivier Hermine[30], Adrien Chauchet[31], Laura Herbreteau[32], Blandine Guffroy[33], Justine Decroocq[34], Steven Le Gouill[35], Roch Houot[6], Estelle Bourbon[5]

[1]Hematology and Cellular Therapy Department, Hôpital Saint-Antoine, Paris, France
[2]Biostatistics Department, LYSARC, Lyon, France
[3]Hematology Department, Centre Hospitalo-Universitaire de Montpellier, Montpellier, France
[4]Hematology Department, Centre Hospitalo-Universitaire de Bordeaux, Bordeaux, France
[5]Hematology Department, Hospices Civils de Lyon, Pierre Bénite, Lyon, France
[6]Hematology and Cell Therapy Department, Centre Hospitalo-Universitaire de Rennes, Rennes, France
[7]Hematology Department, Institut Paoli-Calmettes, Marseille, France
[8]Hematology Department, Hôpital Saint Louis, Paris, France

[9]Hematology Department, Centre Hospitalo-Universitaire de Poitiers, Hôpital la Milétrie, Poitiers, France

[10]Hematology and Cell Therapy Department, Centre Hospitalo-Universitaire de Tours, Tours, France

[11]Hematology Department, Centre Henri Becquerel, Rouen, France

[12]Hematology Department, Centre Hospitalo-Universitaire de Nantes, Nantes, France

[13]Hematology Department, Hôpital Henri Mondor, Créteil, Paris, France

[14]Hematology Department, Centre Hospitalo-Universitaire de Lille, Lille, France

[15]Hematology Department, Centre Hospitalo-Universitaire de Dijon, Dijon, France

[16]Hematology Department, Gustave Roussy Institute, Villejuif, France

[17]Hematology Department, Centre Hospitalo-Universitaire de Toulouse, Toulouse, France

[18]Hematology Department, Centre Hospitalo-Universitaire de Nice, Nice, France

[19]Hematology Department, Hôpital Pitié-Salpêtrière, Paris, France

[20]Hematology Department, Centre Hospitalo-Universitaire de Caen, Caen, France

[21]Hematology Department, Centre Hospitalo-Universitaire de Nancy, Nancy, France

[22]Hematology Department, Centre Hospitalo-Universitaire de Angers, Angers, France

[23]Hematology Department, Centre Hospitalo-Universitaire de Clermont-Ferrand, Clermont-Ferrand, France

[24]Hematology Department, Centre Hospitalo-Universitaire de Amiens, Amiens, France

[25]Hematology Department, Centre Hospitalo-Universitaire de Grenoble, Grenoble, France

[26]Hematology Department, Leon Berard Center, Lyon, France

[27]Hematology Department, Centre Hospitalo-Universitaire de Limoges, Dupuytren Hospital, Limoges, France

[28]Hematology Department, Hôpital d'instruction Des Armées, Percy, France

[29]Hematology Department, Centre Hospitalo-Universitaire de Saint Etienne, Saint Etienne, France

[30]Hematology Department, Hôpital Necker Enfants Malades, Paris, France

[31]Hematology Department, Centre Hospitalo-Universitaire de Besançon, Besançon, France

[32]Hematology Department, Centre Hospitalo-Universitaire de Brest, Brest, France

[33]Hematology Department, Centre Hospitalo-Universitaire de Strasbourg, Strasbourg, France

[34]Hematology Department, Hôpital Cochin, Paris, France

[35]Hematology Department, Curie Institute, Paris, France

Corresponding author:
Antoine CAPES
antoinecapes@gmail.com

ACKNOWLEDGEMENTS
The authors thank the patients whose data were collected in the DESCAR-T registry and their families. They also thank each member of the LYSARC DESCAR-T study group who actively participated in the study, and notably A. Cuozzo and V. Dupont from the biostatistics department, A. Marquet, H. Tonoli and H. Hafirassou for their precious contributions.

AUTHORSHIP
Contribution: A.C. and E.B. contributed equally to this study by designing the research and writing the paper. C.R. and E.G. performed all statistical analysis. All authors provided study material and patients, provided final reading and approval for the article, and are accountable for all aspects of the work.

AUTHORS' DISCLOSURE
AC reports travel grants or honoraria from Bristol Myers Squibb/Celgene, Takeda, Gilead/Kite. EBo reports honoraria from SOBI, Gilead/Kite, Pierre Fabre. EBa reports honoraria from AbbVie, Roche, Takeda, ADC Therapeutics, BeiGene, Bristol Myers Squibb, Incyte, Janssen, Kite, Novartis and Pfizer, and research funding from Amgen. GM reports honoraria from Gilead, Novartis, Abbvie, Roche, BMS, Incyte, Takeda. AD reports advisory board from Gilead and Novartis. GD reports research grant from Takeda, Ideogen; travel grants from Takeda, Menarini and education grant from Kite, Amgen. RH has received honoraria from Gilead/Kite, Novartis, Bristol-Myers Squibb/Celgene, Incyte, Janssen, MSD, Takeda, Amgen, Abbvie, and Roche; and is a member on an entity's Board of Directors or advisory committees of Gilead/Kite, Novartis, Bristol-Myers Squibb/Celgene, Tessa Therapeutics, Abbvie and Roche. BT declares travel grants from Gilead/Kite. GC reports consultancies from Roche, Celgene-BMS, Abbvie, Incyte, BeOne; scientific advisory boards from Onwards Therapeutics, MedxCell, EmerCell, MabQi and honoraria from Sanofi, Abbvie, Takeda, Roche, Janssen, Roche, BMS, Gilead, Novartis, Incyte, BeOne. ML reports honoraria from Novartis, BMS, AbbVie, Gilead, GSK, AOP Orphan, Menarini Stemline, Jazz. SC reports honoraria from Gilead-kite, Novartis, BMS, J&J, BeOne, AMGEN, Pierre Fabre, Takeda, Serb. FM reports consulting fees from Bristol Myers Squibb, Roche/Genentech, Janssen, Ipsen,Takeda, AstraZeneca, Abbvie, Kite/Gilead and research funding from Bristol Myers Squibb, Roche/Genentech, Abbvie, Kite/Gilead. PB has received honoraria from Gilead Kite. OH declares travel grants from Gilead/Kite. The remaining authors report no conflicts.

DATA SHARING
Data are available upon reasonable request.

AI USE DECLARATION
AI use was restricted to the correction of English spelling and grammar.

CLINICAL TRIAL DETAILS
The French Register Of Patients With Hemopathy Eligible For CAR-T Cell Treatment (DESCAR-T) is a registry including prospective and retrospective data on all patients who have been presented in a French multidisciplinary tumor board (RCP) to be eligible for CAR-T cell treatment. ClinicalTrials.gov ID: NCT04328298.

ABSTRACT (247/250 words)

The optimal approach for holding or bridging therapy (H/BT) prior to second line axicabtagene ciloleucel (axi-cel) remains undefined, and the prognostic impact of response to H/BT remains debated. Here, we characterize real-world H/BT strategies and evaluate the impact of response on outcome following axi-cel infusion in the second-line setting for relapse or refractory (R/R) large B-cell lymphoma (LBCL). We included all adults with R/R LBCL within 12 months of first-line therapy who received axi-cel in the nationwide French DESCAR-T cohort (NCT04328298). The primary objective was to EFS between H/BT responders and non-responders, as per Lugano criteria, using propensity score matching (PSM). Secondary objectives were to characterize H/BT modalities, corresponding responses, and to identify predictors of EFS at infusion. Among 566 patients included, 469 (83%) received chemotherapy-based H/BT, while 97 (17%) received a chemo-free approach, including no H/BT. Patients treated with chemotherapy-based H/BT had more advanced disease characteristics and exhibited inferior EFS compared to those receiving chemo-free approaches. After PSM, OS was significantly improved in responders versus non-responders (HR=0·70 [95% CI 0·51–0·96], p=0·0292), while the EFS benefit no longer reached statistical significance (HR=0·86 [95%CI 0·70-1·07], p=0·1739). Given that only patients ultimately receiving axi-cel were analyzed, the impact of H/BT response may have been underestimated. A predictive score combining response to H/BT, international prognostic index, LDH, and CRP at infusion identified two risk groups with significantly different EFS. In conclusion, H/BT response appears to be associated with axi-cel outcomes particularly when combined to inflammatory markers and residual LDH.

Key points

- In this cohort, response to H/BT was associated with better overall survival.
- Progressive disease after H/BT emerged as the key driver of poor outcomes.
- A prognostic score combining response to H/BT, international prognostic index, LDH, and CRP at infusion identified two risk groups with significantly different EFS.

INTRODUCTION

Chimeric antigen receptor (CAR) T cell therapy represents a major advancement in the treatment of relapsed and refractory (R/R) large B-cell lymphomas (LBCL).[1–5] The approval of two anti-CD19 CAR T cell products, axicabtagene ciloleucel (axi-cel) and lisocabtagene maraleucel (liso-cel), in the second-line (2L) setting has challenged the long-standing paradigm of autologous stem cell transplantation as the standard of care, demonstrating significantly improved patient outcomes.[6,7]

Upon CAR T cell eligibility, patients may receive holding therapy (HT), administered prior to leukapheresis, or bridging therapy (BT), given between leukapheresis and infusion.[8,9] Although not systematically administered, holding or bridging therapy (H/BT) is frequently employed to limit rapid disease progression during CAR T manufacturing. In the ZUMA-7 study,[6] optional bridging therapy was limited to steroids only, whereas in the TRANSFORM trial,[7] broader bridging options were permitted.

In the second line setting, no optimal H/BT approach has been established, and treatment selection varies across centers, expected time to infusion, disease burden and specific comorbidities.[10]

The impact of H/BT on CAR T cell outcome has been mostly documented in the third line setting and more, where data suggest that effective disease control with reduced tumor burden improves survival outcomes after CAR T cell infusion.[8,9,11,12] One study further stratified outcomes by CAR T product and showed that response to bridging therapy was

associated with a lower risk of progression after tisagenlecleucel (tisa-cel), but this association did not reached statistical significance with axi-cel.[13]

To date, the impact of response to H/BT on outcome in second-line CAR T cell therapy has not been specifically addressed, and it remains unclear whether deepening response prior to infusion is required.

We conducted a retrospective analysis using the nationwide French DESCAR-T registry to evaluate the impact of H/BT response on 2L axi-cel efficacy. Secondary objectives were to characterize H/BT modalities and corresponding outcomes, assess the impact of delayed vein-to-vein time (V2Vt), and identify prognostic factors of event-free survival (EFS) at infusion.

METHODS

Study population

We conducted a registry-based study of adult patients with LBCL who developed R/R disease within 12 months of first-line chemoimmunotherapy and subsequently received standard-of-care axi-cel, as recorded in the French DESCAR-T registry. Patients who underwent leukapheresis but did not receive CAR T-cell infusion were excluded because outcome data were unavailable. The study was approved by the relevant national ethics committees and data protection authority and conducted in accordance with the Declaration of Helsinki. DESCAR-T is registered at ClinicalTrials.gov (NCT04328298).

Holding/bridging therapy definition and classification

Holding therapy was defined as any treatment administered after the decision to proceed with CAR T-cell and before leukapheresis. The date of CAR T-cell therapy decision was defined as the date of the multidisciplinary tumor board at which CAR T-cell therapy was recommended. Bridging therapy was defined as any treatment administered after leukapheresis and before CAR T-cell infusion.

Holding and bridging treatments were categorized into four groups: chemotherapy, radiotherapy, targeted therapy, and steroids. In cases where patients received combined H/BT modalities, classification was assigned according to the following hierarchical order: chemotherapy > radiotherapy > targeted therapy > steroids.

Endpoints

The primary endpoint was EFS, defined as the time from the CAR T-cell infusion to occurrence of the first documented progression, failure to achieve a response at 3-months, initiation of a new treatment for non-responders or death, without prior progression, whichever occurred first. Secondary endpoints were overall survival (OS) and response to H/BT according to the Lugano 2014 criteria[10] based on FDG-PET performed and interpreted locally in each center prior to infusion, at 1, 3, 6 and 12-months after CAR T infusion.

Safety endpoints included cytokine release syndrome (CRS) and immune-cell associated neurotoxicity syndrome (ICANS), graded according to the American Society for Transplantation and Cellular Therapy consensus criteria.[14]

Statistical analysis

Clinical characteristics were compared according to H/BT regimen using the χ^2 test or the Wilcoxon rank-sum test. Survival was estimated using the Kaplan–Meier method and compared with the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models.

To account for baseline differences between H/BT response groups, a propensity score-weighted analysis was performed using a gradient-boosted logistic regression model (twang R package)[15,16] (**Supplementary Methods, Supplementary Table 1 and 2, Supplementary Figure 1**). Missing data were handled by multiple imputation using fully conditional specification (50 datasets). Covariate balance after weighting was assessed using the maximum pairwise absolute standardized mean difference.

A prognostic score for EFS was developed using a multivariable Cox model including clinically relevant variables: age, age-adjusted International Prognostic Index, Ann Arbor stage, de novo versus transformed LBCL, H/BT response, bulky disease, lactate dehydrogenase, C-reactive protein at lymphodepletion. Variables with $P<0.20$ were retained. HRs were rescaled relative to the smallest HR, and weighted points were assigned according to their relative prognostic impact. Individual scores were calculated by summing these points, with higher scores indicating poorer prognosis.

The optimal V2Vt cut-off for survival discrimination was determined using maximally selected rank statistics (maxstat R package)[17]. Analyses were performed using SAS version 9.4 and R version 4.5.2.

RESULTS

Patients' characteristics and outcome

Between July 2022 and March 2024, 566 patients with R/R LBCL within one year of first-line therapy with available H/BT information and registered in the DESCAR-T registry across 33 French centers received axi-cel (**Figure 1**).

Patient characteristics are presented in **Table 1**. At the time of CAR T eligibility, median age was 61 years (range 18-82) and 64% were males, most patients had advanced stage disease (431/566 [76%]), elevated LDH (336/566 [59%]) and a refractory disease (421/566 [74%]). Histological diagnosis was DLBCL not otherwise specified (NOS) for most patients (442/566 [78%]); other diagnosis included transformed indolent lymphoma (71/566 [13%]), high-grade B-cell lymphoma (30/566 [5%]), and primary mediastinal large B cell lymphoma (17/566 [3%]). Among biochemical parameters at the time of CAR T infusion, 260/566 patients (46%) had elevated LDH, 281/566 (50%) had high ferritin and 92/566 (16%) had a CRP superior to 30mg/L.

Comparison of the 566 infused patients with the 69 non-infused patients showed that non-infused patients had poorer performance status (ECOG≥2, 20% vs 10%; p=0·010) and were less likely to have received H/BT (75% vs 91%, p<0·001), with a lower response rate (CR/PR, 19% vs 45%, p<0·001) (**Supplementary Table 3**).

Among the 566 patients infused, with a median follow-up of 6.3 months (95% CI 6.1-6.5) since first infusion, one-year OS and EFS were 70% (95% CI 64·1-75·0) and 52% (95% CI 46·8-56·9), respectively (**Figure 2**).

Holding and bridging therapy

H/BT was administered to 514/566 (91%) patients, most of whom received bridging therapy alone (398/514 [70%]), a smaller proportion received holding therapy alone (76/514 [13%]) or both holding and bridging therapy (40/514 [7%]) (**Figure 1**). Most patients received only one line of holding (110/514 [95%]) or bridging therapy (398/514 [91%]) (**Supplementary Table 4**).

Among patients receiving H/BT, 469/514 (91%) were treated with chemotherapy-based regimens, most often as monotherapy (412/469 [88%]) and rarely in combination with immunotherapies or targeted therapies (57/469 [12%]) (**Supplementary Table 5**). These consisted predominantly of nucleoside analog-based therapies (303/469 [65%]), the majority of which included high-dose cytarabine (258/303 [85%]). Alkylating agent-based regimens were used less frequently (147/469 [31%]), and were mainly ifosfamide-based combinations (142/147 [97%]). Regarding treatment intensity, most patients (324/469 [69%]) received high-intensity regimen while 31% (145/469) had a low-intensity regimen. Age was the only significant difference between the two groups, with patients receiving high-intensity regimens being younger than those receiving low-intensity regimens (median age, 60 vs. 67 years, respectively; $P < 0.001$) (**Supplementary Table 6, 7 and 8**).

Chemo-free H/BT approaches included radiation therapy (30/514 [6%]), targeted therapies (11/514 [2%]), and steroids (4/514 [<1%]) (**Supplementary Table 5**). Regarding targeted therapies and immunotherapies, 21/514 (4%) patients received immunomodulatory drug lenalidomide, 18/514 (4%) received Bruton Tyrosine Kinase inhibitors (BTKi) ibrutinib and 11/514 (2%) received anti-CD3xCD20 bispecific T-cell engager (BITE), as a single agent either alone or in combination with chemotherapy (**Supplementary Table 9**).

Only 52/566 (9%) patients did not receive any waiting therapy.

Following H/BT, response to H/BT was assessed at a median of 8 days before lymphodepletion and 13 days before CAR T infusion (inter-quartile range: 4-11 and 9-17 days respectively). The overall response rate (ORR) was 46·7% [95% CI 42·2%; 51·3%], including Complete Response (CR) in 15·3% and Partial Response (PR) in 31·4%. Non-response rate was 53·3%, with 12·2% of Stable Disease (SD) and 41·1% of Progressive Disease (PD) **(Supplementary Tables 10 and 11**).

Outcome according to H/BT regimen

Patients were categorized based on whether they received a chemo-based H/BT or chemo-free approaches (i.e. chemo-free H/BT or no H/BT). Comparing baseline characteristics, chemo-based H/BT treated patients had more advanced stage disease (stage III-IV: 79% vs 64%, p=0·0128), higher LDH (LDH>UNL: 63% vs 43%, p=0·0026) and aaIPI (2-3: 50% vs 31%, p=0.009) (**Table 2**). EFS and OS were significantly higher in the chemo-free approach compared to the chemo-based group (12-months EFS: 64·1% versus 49·3%, HR=0·62 [95% CI 0·42-0·92], p=0·012; 12-months OS: 74·8% versus 69·2%, HR=0·55 [95% CI 0·31-0·98], p=0·0286 respectively) (**Figure 3; Supplementary Table 12**).

Among chemo-based H/BT, there were no significant differences in survival outcomes across the two main chemotherapy regimens, that are nucleoside analogs or alkylating agents (12 months EFS: 47.8% versus 52.2%, HR=1.16 [95% CI 0·84-1·59], p=0·3615; 12 months OS: 66·2% versus 75%, HR=1·31 [95% CI 0·82-2·09], p=0·2469 respectively) (**Figure 3**; **Supplementary**

Table 13). When comparing treatment intensity, no significant differences in survival were observed between the two groups (**Figure 3**).

Patients receiving radiation therapy demonstrated 1-year EFS and OS of 73·8% (95% CI 52·6-86·6) and 76·6% (95% CI 39·9-92·6) respectively (**Supplementary Figure 1**).

Among patients receiving a single immunotherapy or targeted therapy agent for H/BT, either alone or in combination with chemotherapy, the 1-year EFS was 53·3% (95% CI 12·5-82·7) for those treated with T cell engagers, 45·9% (95% CI, 21·6-67·4) for those receiving BTKi and 37% (95% CI 15·1-59·2) for patients treated with IMIDs (**Supplementary Figure 2**).

Impact of response to H/BT

In unmatched comparisons, patients achieving CR or PR had significantly higher EFS (12-months EFS: 58·3 versus 46·5%, HR=0·68 [95% CI 0·50-0·91], p=0·0084) and OS (12-months OS: 79·2% versus 62·7%, HR=0·47 [95% CI 0·30-0·74], p=0·0006) than those with SD or PD (**Figure 4; Supplementary Figure 3 and Supplementary Table 14**).

In the weighted analysis after PSM, progressive disease emerged as the key driver of poor outcomes since CR, PR, and SD were each associated with significantly improved EFS compared to PD (HR=0·72 [95% CI 0·53-0·99], p=0·0458; HR=0·77 [95% CI 0·61-0·97], p=0·003 and HR=0·71 [95% CI 0·54-0·95], p=0·0198 respectively) (**Supplementary Table 15**).

Responders continued to demonstrate significantly better OS than non-responders (HR=0·70 [95% CI 0·51–0·96], p=0·0292) whereas EFS difference was no longer statistically significant (HR=0·86 [95% CI 0·70–1·07], p=0·1739). (**Figure 4**).

Prognostic score for EFS following H/BT

Among the clinical variables considered for building the prognostic score, multivariate analysis identified four clinically relevant factors (response to H/BT, aaIPI >1, LDH, and CRP at infusion) showing associations with a p-value < 0·20, which were subsequently retained for model construction. This scoring system stratified patients into two groups (0–1 vs 2-4) with distinct EFS profiles. Patients with a score of 0-1 demonstrated significantly improved EFS compared with those scoring 2-4 (12-months EFS: 60·4% versus 38·7%, HR=2·08 [95% CI 1·57-2·75], p<0·0001) (**Figure 5**).

Vein-to-vein time

Median V2Vt was 37 days (range 18-170). A recent large US real-world study identified a 40-day cut-off as discriminant for survival. When applying this threshold to our cohort, we did not observe significant differences in either EFS or OS (**Supplementary Figure 4**). Using a cut-off optimization approach, we found that no value of V2Vt robustly separated patients with respect to OS and EFS.

Toxicities

Among patients evaluated for safety (n=555), 519 (94%) presented a CRS, among which 26 (5%) where grade 3 or more. ICANS were reported in 264 (48%) patients, 94 (17%) being grade 3 or more.

Among patients evaluable for safety and response to H/BT (n = 475), severe CRS occurred in 4% of responders and 6% of non-responders, severe neurotoxicity was observed in 16% and

19%, respectively, and non-relapse mortality was 4% in responders compared with 8% in non-responders.

DISCUSSION

This multicenter retrospective study is the largest real-world evaluation of bridging therapy prior to axi-cel infusion in LBCL, and the first dedicated exclusively to the 2L setting. In this cohort, the 1-year OS and EFS rates were 70% and 52%, respectively, which are comparable to the results reported in the ZUMA-7 trial.[6]

In this second-line French cohort, the vast majority of patients (91%) received a H/BT prior to axi-cel infusion. This markedly differs from published U.S. cohorts, where the use of H/BT was more limited[8,10,18,19]. In a multicenter analysis, Jain et al. reported improved OS and PFS among patients who did not receive bridging therapy; however, this benefit was not confirmed after PSM.[10] We adopted a slightly different approach by comparing chemo-free strategies (including no H/BT) with chemo-based H/B regimens and observed improved OS and EFS in the chemo-free group. These findings should be interpreted with caution since chemo-free patients had less advanced disease at the time of 2L treatment decision, precluding definitive conclusions from this direct comparison. Nevertheless, our findings suggest that in a carefully selected subset of patients, intensive chemo-based bridging therapy may not be required.

To further explore treatment heterogeneity, we analyzed chemotherapy-based regimens according to the main agents used and treatment intensity, with no significant differences observed between groups. Nevertheless, the broad categorization of H/BT approaches may have masked clinically relevant differences between specific regimens.

Interpretation of our finding should also take into account the treatment landscape during the study period. Polatuzumab vedotin was not available, and only a small number of patients received T cell engagers. This is particularly relevant given the efficacy reported with these two newer approaches in R/R LBCL.[20,21]

We performed a PSM analysis incorporating variables at CAR-T eligibility but also measures of tumor burden and inflammation at the time of lymphodepletion to determine the association between Lugano response criteria for post-infusion outcomes. Our results suggest a benefit for responders, although with some inconsistencies. Specifically, partial response was associated with improved OS and EFS compared with progressive disease, whereas complete response was only associated with better OS. Furthermore, when comparing responders with non-responders, response to H/BT was associated with better OS, while the association with EFS lost its statistical significance upon PSM.

Several points regarding these results warrant further discussion. First, this analysis evaluates the effect of bridging response on axi-cel efficacy among patients who ultimately underwent CAR T-cell infusion. This selection bias likely underestimates the beneficial effect of H/BT response. Second, these findings may reflect limited statistical power. Third, it could indicate that the Lugano criteria alone are not optimally suited to predict EFS following CAR T-cell therapy. Indeed, these criteria were developed in the pre–CAR T era to assess chemosensitivity, which was particularly relevant when high-dose chemotherapy followed by autologous stem cell transplantation represented the standard of care in second line. In the CAR T era, emerging data suggest that other factors, such as metabolic tumor volume (MTV) and inflammatory markers, are strong predictors of outcome.[22–24] Fourth, since the majority of patients received chemo-based H/BT, response was largely determined by

chemosensitivity. This parameter may have served as a surrogate for later treatment response, which could explain why OS was more affected than EFS. Fifth, response to H/BT may capture underlying disease biology that influence sensitivity to subsequent cellular therapy. Finally, despite the comprehensive propensity score model, treatment allocation was not randomized and unmeasured confounding related to physician decision-making cannot be excluded, results should therefore be interpreted as associative rather than causal.

Although MTV was unavailable during the study period, multivariable analysis allowed us to develop an EFS predictive score integrating surrogates of tumor burden (LDH at infusion and aaIPI at 2L decision), systemic inflammation at infusion, and response to H/BT. This score effectively discriminated patients according to EFS after infusion. Importantly, even patients in the highest risk group had survivals comparable to that reported in third line and beyond,[10] underscoring the curative potential of CAR-T cell therapy despite suboptimal disease control. This score was developed and assessed in the same cohort without internal or external validation and should therefore be considered exploratory, its clinical utility requires confirmation in independent cohorts.

In a recent analysis of the Center for International Blood and Marrow Transplant Research (CIBMTR) database, Locke et al. demonstrated a significant decrease in OS among patients with a V2Vt exceeding 40 days.[19] In our cohort, no value of V2Vt robustly separated the population with respect to OS and EFS. These discrepancies may be explained by differences in patient populations, as our study focused exclusively on 2L disease, whereas the CIBMTR analysis included later-line settings, in which disease kinetics may be more aggressive. Moreover, it is important to note strong limitations when assessing V2Vt impact. As discussed

above, our analysis included only patients who ultimately received CAR-T cell infusion, thereby excluding patients who may have died before infusion because of prolonged delays. This selection bias likely underestimates the detrimental impact of prolonged V2Vt and was also present in the CIBMTR study. Moreover, the reasons for delayed infusion were incompletely reported in our registry, preventing robust conclusions regarding the causes of delay. Nonetheless, available data on out-of-specification products and manufacturing failures indicated that these were infrequent contributors. Additionally, the V2Vt does not fully capture the interval from CAR T decision to infusion in patients receiving holding therapy since holding may delay apheresis.

On top of the aforementioned limitations, in this study the follow-up was limited. Median follow-up from CAR T-cell infusion was 6.2 months, with 86 patients remaining at risk at 1 year. Although most events occurred within the first 6 months, longer follow-up will be needed to better characterize long-term outcomes and late events.

Finally, this study was not designed to establish treatment guidelines, and our findings, although clinically relevant, should therefore be interpreted with caution.

In summary, progressive disease after H/BT emerged as the key driver of poor outcomes after second-line axi-cel in LBCL. Response to H/BT per Lugano criteria was associated with improved OS. It was also associated with better EFS in unmatched analysis, although it was no longer significant after PSM. In contrast, a composite model incorporating response to H/BT, IPI, tumor burden, and marker of systemic inflammation at infusion strongly predicted EFS.

REFERENCES

1. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: Results from the international SCHOLAR-1 study. Blood. 2017;130(16):1800-1808.

2. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2019;380(1):45-56.

3. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory Large B-cell lymphoma. N Engl J Med. 2017;377(26):2531-2544.

4. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet. 2020;396(10254):839-852.

5. Neelapu SS, Jacobson CA, Ghobadi A, et al. Five-year follow-up of ZUMA-1 supports the curative potential of axicabtagene ciloleucel in refractory large B-cell lymphoma. Blood. 2023;141(19):2307-2315.

6. Locke FL, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma. N Engl J Med. 2022;386(7):640-654.

7. Kamdar M, Solomon SR, Arnason J, et al. Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial. Lancet. 2022;399(10343):2294-2308.

8. Bücklein V, Perez A, Rejeski K, et al. Inferior outcomes of EU versus US patients

treated with CD19 CAR-T for relapsed/refractory large B-cell lymphoma: association with differences in tumor burden, systemic inflammation, bridging therapy utilization, and CAR-T product use. Hemasphere. 2023;7(8):e907.

9. Bethge WA, Martus P, Schmitt M, et al. GLA/DRST real-world outcome analysis of CAR T-cell therapies for large B-cell lymphoma in Germany. Blood. 2022;140(4):349-358.

10. Jain MD, Jacobs MT, Gao F, et al. Bridging therapy with axicabtagene ciloleucel for large B-cell lymphoma: results from the US Lymphoma CAR-T Consortium. Blood Adv. 2024;8(4):1042-1050.

11. Keijzer K, de Boer JW, van Doesum JA, et al. Reducing and controlling metabolic active tumor volume prior to CAR T-cell infusion can improve survival outcomes in patients with large B-cell lymphoma. Blood Cancer J. 2024;14(1):41.

12. Iacoboni G, Sánchez-Salinas MA, Rejeski K, et al. Efficacy and safety of bendamustine-containing bridging therapy in R/R LBCL patients receiving CD19 CAR T-cells. Hemasphere. 2024;8(7):e86.

13. Roddie C, Neill L, Osborne W, et al. Effective bridging therapy can improve CD19 CAR-T outcomes while maintaining safety in patients with large B-cell lymphoma. Blood Adv. 2023;7(12):2872.

14. 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.

15. McCaffrey DF, Ridgeway G, Morral AR. Propensity score estimation with boosted regression for evaluating causal effects in observational studies. Psychol Methods. 2004;9(4):403-425.

16. Ridgeway G, McCaffrey D, Morral A, et al. Toolkit for weighting and analysis of nonequivalent groups: A guide to the twang package. October 2021. Available at https://hdl.handle.net/20.500.11990/10185. Accessed on 2026, Jan 17.

17. Hothorn T, Lausen B. On the exact distribution of maximally selected rank statistics. Comput Stat Data Anal. 2003;43(2):121-137.

18. Nastoupil LJ, Jain MD, Feng L, et al. Standard-of-care axicabtagene ciloleucel for relapsed or refractory large B-cell lymphoma: results from the US lymphoma CAR T consortium. J Clin Oncol. 2020;38(27):3119-3128.

19. Locke FL, Siddiqi T, Jacobson CA, et al. Impact of vein-to-vein time in patients with R/R LBCL treated with axicabtagene ciloleucel. Blood Adv. 2025;9(11):2663-2676.

20. Sehn LH, Hertzberg M, Opat S, et al. Polatuzumab vedotin plus bendamustine and rituximab in relapsed/refractory DLBCL: survival update and new extension cohort data. Blood Adv. 2022;6(2):533-543.

21. Brooks TR, Zabor EC, Bedelu YB, et al. Real-world outcomes of patients with aggressive B-cell lymphoma treated with epcoritamab or glofitamab. Blood. 2025;146(18):2177-2188.

22. Galtier J, Vercellino L, Chartier L, et al. Positron emission tomography-imaging assessment for guiding strategy in patients with relapsed/refractory large B-cell lymphoma receiving CAR T cells. Haematologica. 2023;108(1):171-180.

23. Hubbeling H, Leithner D, Silverman EA, et al. Metabolic tumor volume response after bridging therapy determines chimeric antigen Receptor T-cell outcomes in large B-cell lymphoma. Clin Cancer Res. 2024;30(22):5083-5093.

24. Raj SS, Fei T, Fried S, et al. An inflammatory biomarker signature of response to CAR-T

cell therapy in non-Hodgkin lymphoma. Nat Med. 2025;31(4):1183-1194.

TABLES

Table 1. Patient's characteristics.

	Treated set N=566
At the time of CAR-T eligibility	
Sex Male	360 (64%)
Age at 2L decision (years)	
Median (min; max)	61·0 (18; 82)
Age (2L decision) ≥ 65 years	228 (40%)
ECOG at 2L decision	
0-1	449 (79%)
≥2	47 (8%)
Missing	70 (12%)
aaIPI	
0-1	190 (34%)
2-3	262 (46%)
Missing	114 (20%)
High LDH at 2L decision	
No	220 (39%)
Yes	336 (59%)
Missing	10 (2%)
HCT-CI-Comorbidity	564
At least one HCT-CI-Comorbidity	204 (36%)
Histology	
DLBCL	442 (78%)
Transformed indolent	71 (13%)
HGBL	30 (5%)
PMBL	17 (3%)
Other	6 (1%)
If DLBCL,	
DLBCL, NOS	436 (99%)
T-cell/histiocyte-rich LBCL	6 (1%)
If transformed indolent,	
Transformed FL	46 (65%)
Transformed MZL	15 (21%)
Richter/Transformed CLL	5 (7%)
Other transformed indolent	5 (7%)
Ann Arbor Stage	
I-II	84 (15%)
III-IV	431 (76%)
Missing	51 (9%)
Status before 2L decision	
Refractory	421 (74%)
Relapse	139 (25%)
Missing	6 (1%)
At the time of CAR-T infusion	
Bulky disease (>5cm)	
No	428 (76%)
Yes	113 (20%)
Missing	24 (4%)
LDH>UNL[†]	260 46%
Ferritin>UNL[†]	281 50%
CRP>30mg/L[†]	92 16%

[†]patients with missing data are included in denominator. aaIPI indicates age-adjusted International Prognostic Index; CAR: chimeric antigen receptor; CLL: chronic lymphocytic leukemia; CRP: C-reactive protein; DLBCL: diffuse large B-cell lymphoma; ECOG: Eastern Cooperative Oncology Group; HCT-CI: hematopoietic cell transplantation-specific comorbidity index; FL: follicular lymphoma; HGBL: high grade B-cell lymphoma; LBCL: large B-cell lymphoma; LDH: lactate dehydrogenase; MZL: marginal zone lymphoma; NOS: not otherwise specified; PMBL: primary mediastinal B-cell lymphoma; UNL: upper normal limit; and 2L: second line.

Table 2. Comparison of patient's characteristics according to H/BT status.

	CHEMO-based H/BT N=469		CHEMO-free H/BT NO H/BT N=97		P-value
Age in years: median (min; max)	61·0 (18; 81)		60·0 (22; 82)		P=0·5518
ECOG					P=0·6791
0-1	370	(79%)	79	(81%)	
≥2	42	(9%)	5	(5%)	
Missing	57	(12%)	13	(13%)	
aaIPI					P=0·0090
0-1	146	(31%)	44	(45%)	
2-3	232	(50%)	30	(31%)	
Missing	91	(19%)	23	(24%)	
LDH>UNL					P=0·0026
No	166	(35%)	54	(56%)	
Yes	294	(63%)	42	(43%)	
Missing	9	(2%)	1	(1%)	
At least one HCT-CI-Comorbidity	176	(38%)	28	(29%)	P=0·5518
Ann Arbor Stage					P=0·0128
I-II	60	(13%)	24	(25%)	
III-IV	369	(79%)	62	(64%)	
Missing	40	(9%)	11	(11%)	
Disease status					P=0·9129
Refractory	350	(75%)	71	(73%)	
Relapse	115	(25%)	24	(25%)	
Missing	4	(1%)	2	(2%)	
Bulky disease at lymphodepletion (>5cm)					P=0·1117
No	344	(73%)	84	(88%)	
Yes	102	(22%)	11	(12%)	
Missing	23	(5%)	1	(1%)	
LDH>UNL at infusion†	225	(48%)	35	(36%)	P=0·2095
Ferritin>UNL at infusion†	253	(54%)	28	(29%)	P=<0·0001
CRP > 30mg/L at infusion†	80	(17%)	12	(12%)	P=0·8143

All characteristics are measured at the time of CAR-T cell eligibility, if not otherwise specified. †Patients with missing data are included in denominator· High means up to normal. aaIPI indicates age-adjusted International Prognostic Index; CRP: C-reactive protein; ECOG: Eastern Cooperative Oncology Group; HCT-CI: hematopoietic cell transplantation-specific comorbidity index; LDH: lactate dehydrogenase; and UNL: upper normal limit.

FIGURE LEGENDS

Figure 1. Patient flow diagram.

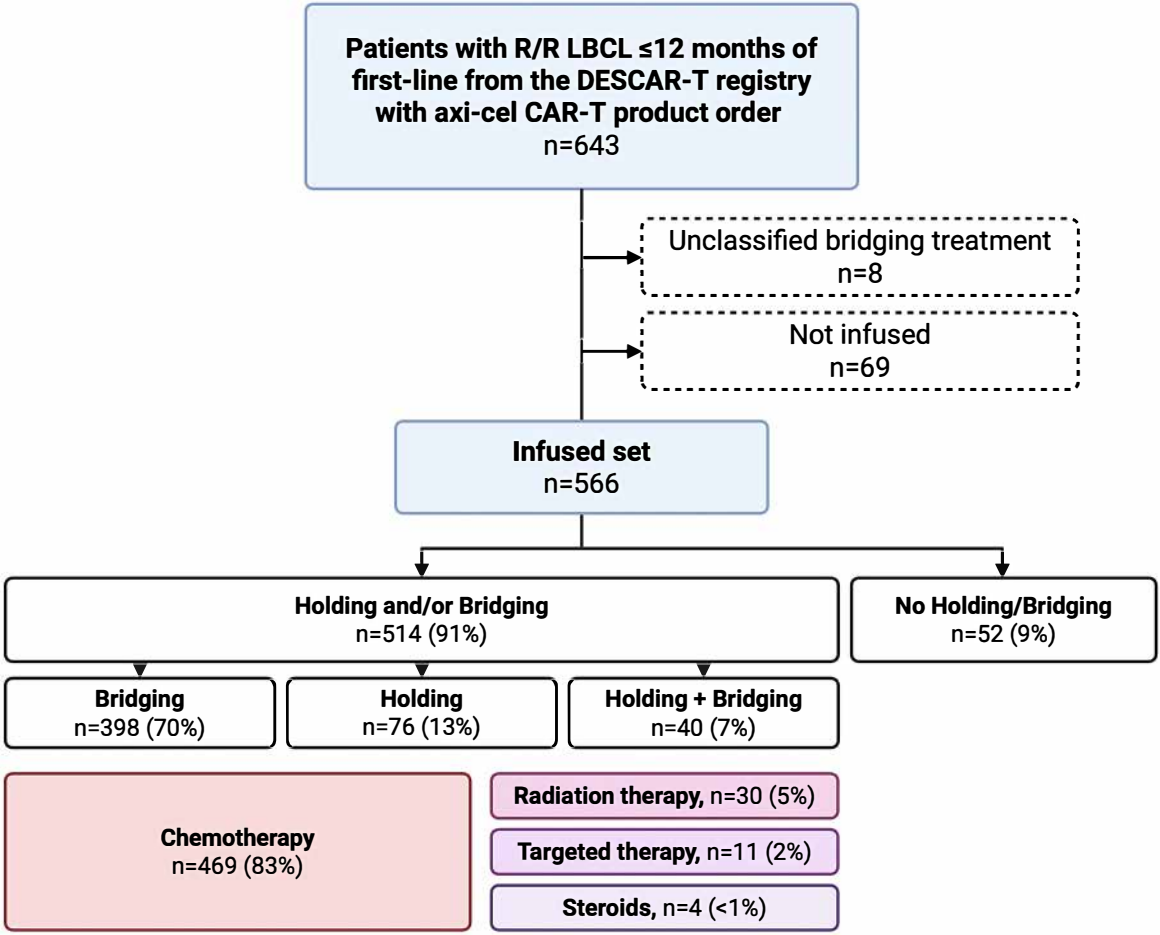
CAR indicates chimeric antigen receptor; H/BT: holding and/or bridging therapy; LBCL: large B-cell lymphoma; and R/R: relapsed or refractory.

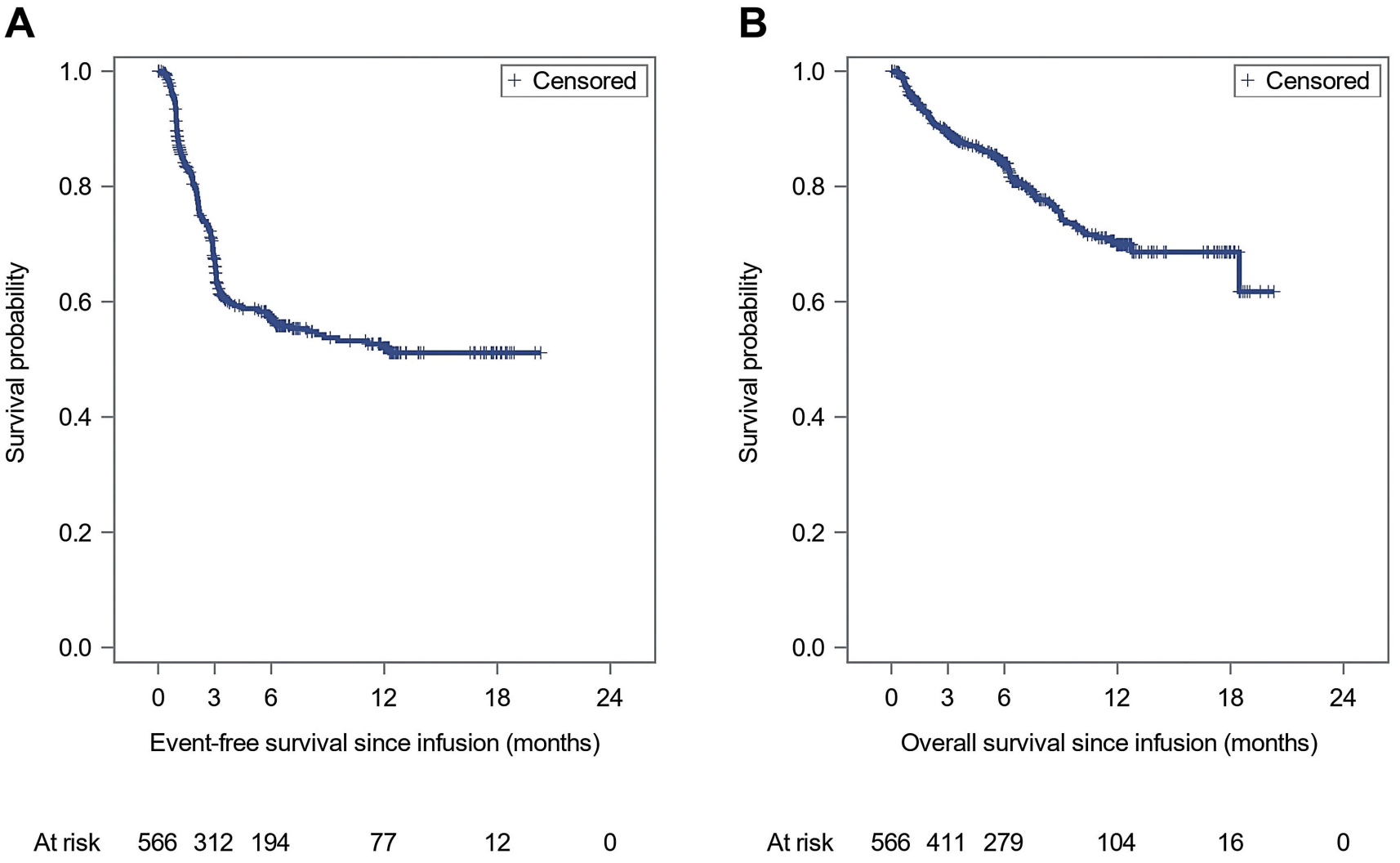
Figure 2. Survivals in the entire study cohort. (A) Event free survival and (B) overall survival in the whole cohort from CAR-T infusion.

Figure 3. Survivals according to holding/bridging therapy. (A) Event free survival and (B) overall survival in chemo-based versus chemo-free H/BT. (C) Event free survival and (D) overall survival in alkylating agent-based versus nucleoside analog-based H/BT. H/BT indicates holding and/or bridging therapy. (E) Event free survival and (F) overall survival based on H/BT intensity.

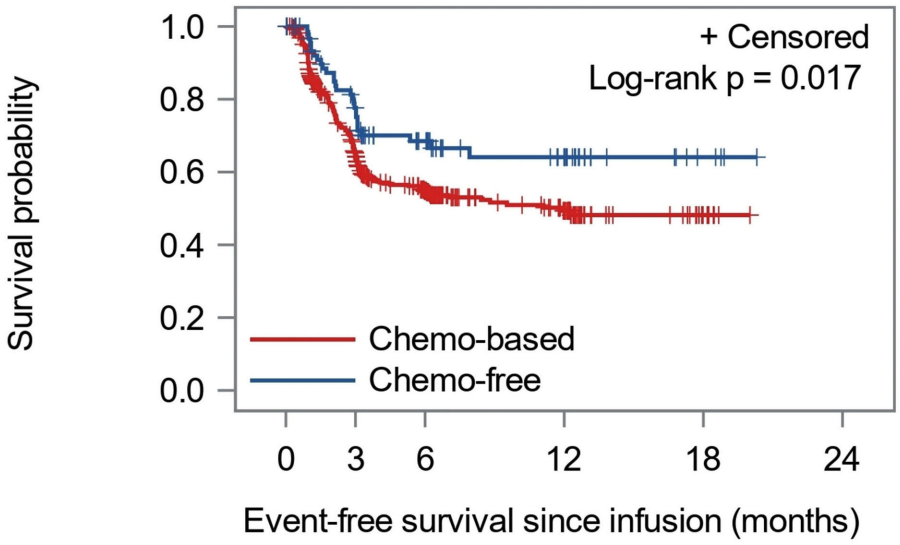
Figure 4. Impact of response to holding/bridging therapy on survival. (A) Event free survival (EFS) and (B) overall survival (OS) according to H/BT response in the unmatched population. (C) Forest plot hazard ratios (HR) for EFS and OS comparing responders (CR or PR) with non-responders (SD or PD) to H/BT, in unmatched and propensity-score matched analysis.

Figure 5. Event free survival based by score-based risk stratification. The red curve indicates patients with an EFS score of 0 to 1, while the blue curve represents patients with a score of 2 or more.


Patients with R/R LBCL ≤12 months of first-line from the DESCAR-T registry with axi-cel CAR-T product order
n=643
Unclassified bridging treatment
n=8
Not infused
n=69
Infused set
n=566
Holding and/or Bridging
n=514 (91%)
No Holding/Bridging
n=52 (9%)
Bridging
n=398 (70%)
Holding
n=76 (13%)
Holding + Bridging
n=40 (7%)
Chemotherapy
n=469 (83%)
Radiation therapy, n=30 (5%)
Targeted therapy, n=11 (2%)
Steroids, n=4 (<1%)

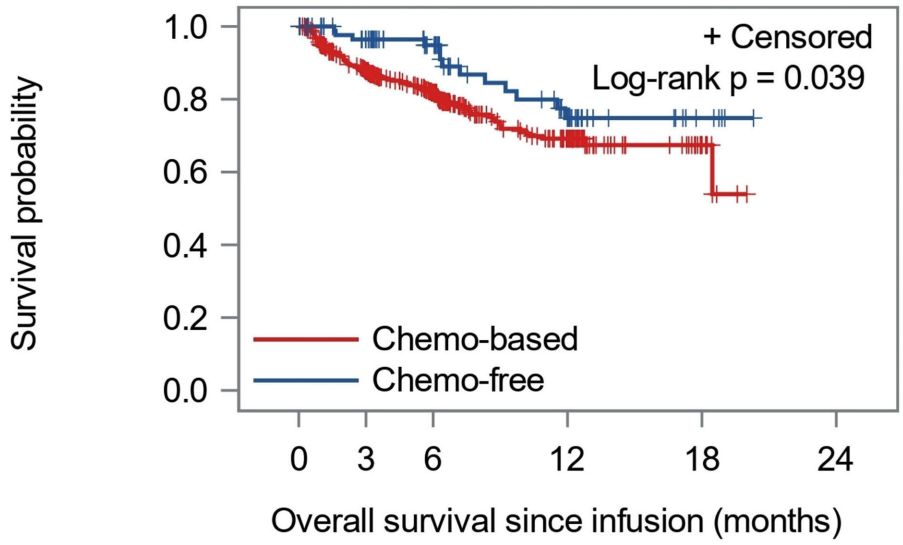

A
B
Censored
Survival probability
1.0
0.8
0.6
0.4
0.2
0.0
0
3
6
12
18
24
Event-free survival since infusion (months)
Overall survival since infusion (months)
At risk 566 312 194 77 12 0
At risk 566 411 279 104 16 0

A



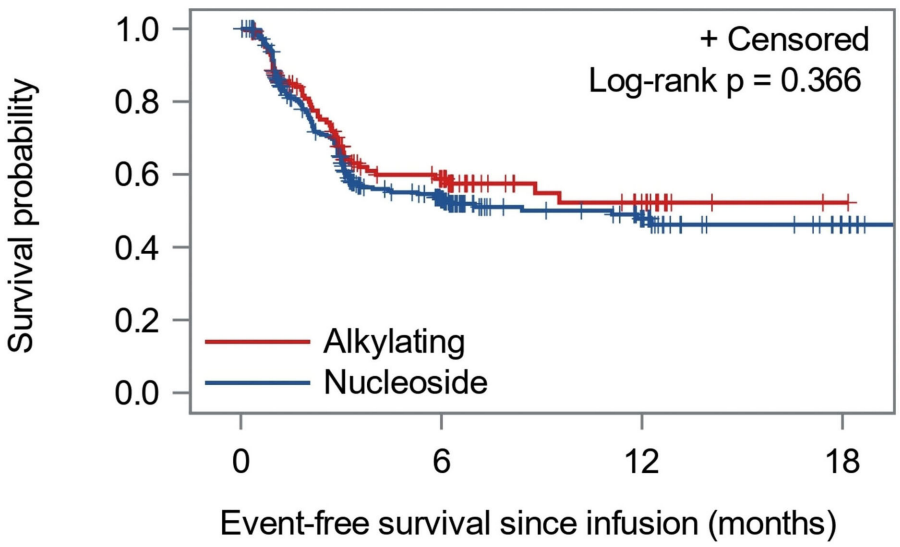
Chemo-based	469	250	154	55	8	0
Chemo-free	97	62	40	22	4	0

B



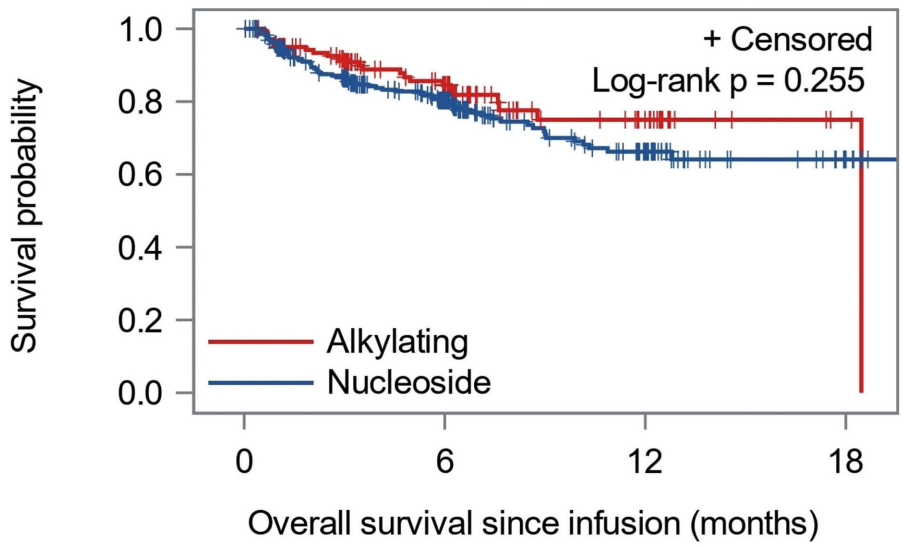
Chemo-based	469	334	223	77	11	0
Chemo-free	97	77	56	27	5	0

C



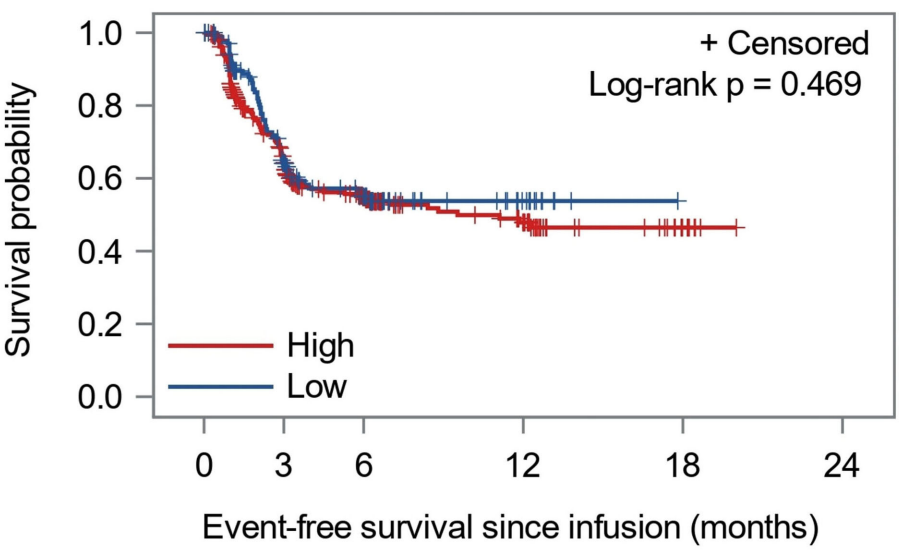
Alkylating	147	51	14	1
Nucleoside	303	99	39	7

D



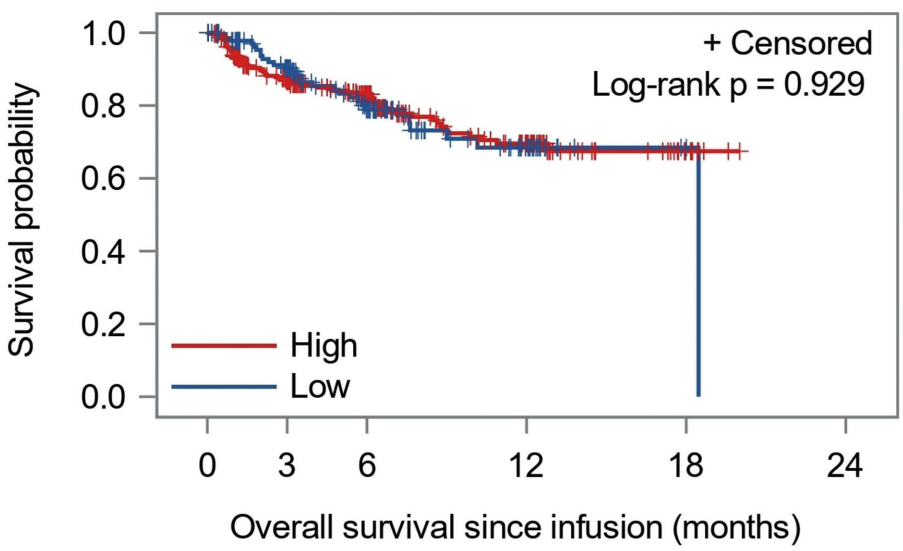
Alkylating	147	74	19	2
Nucleoside	303	144	56	9

E

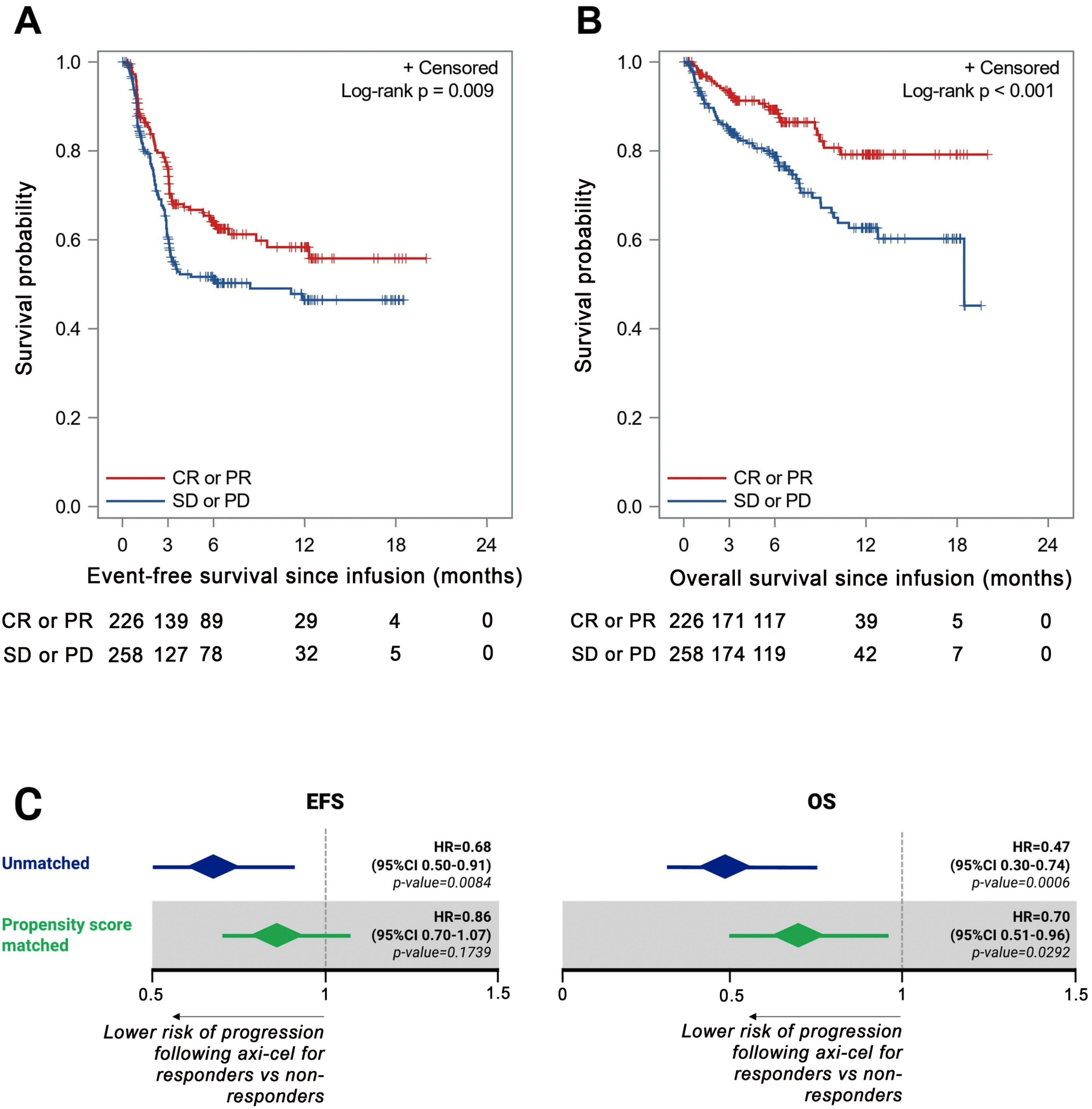


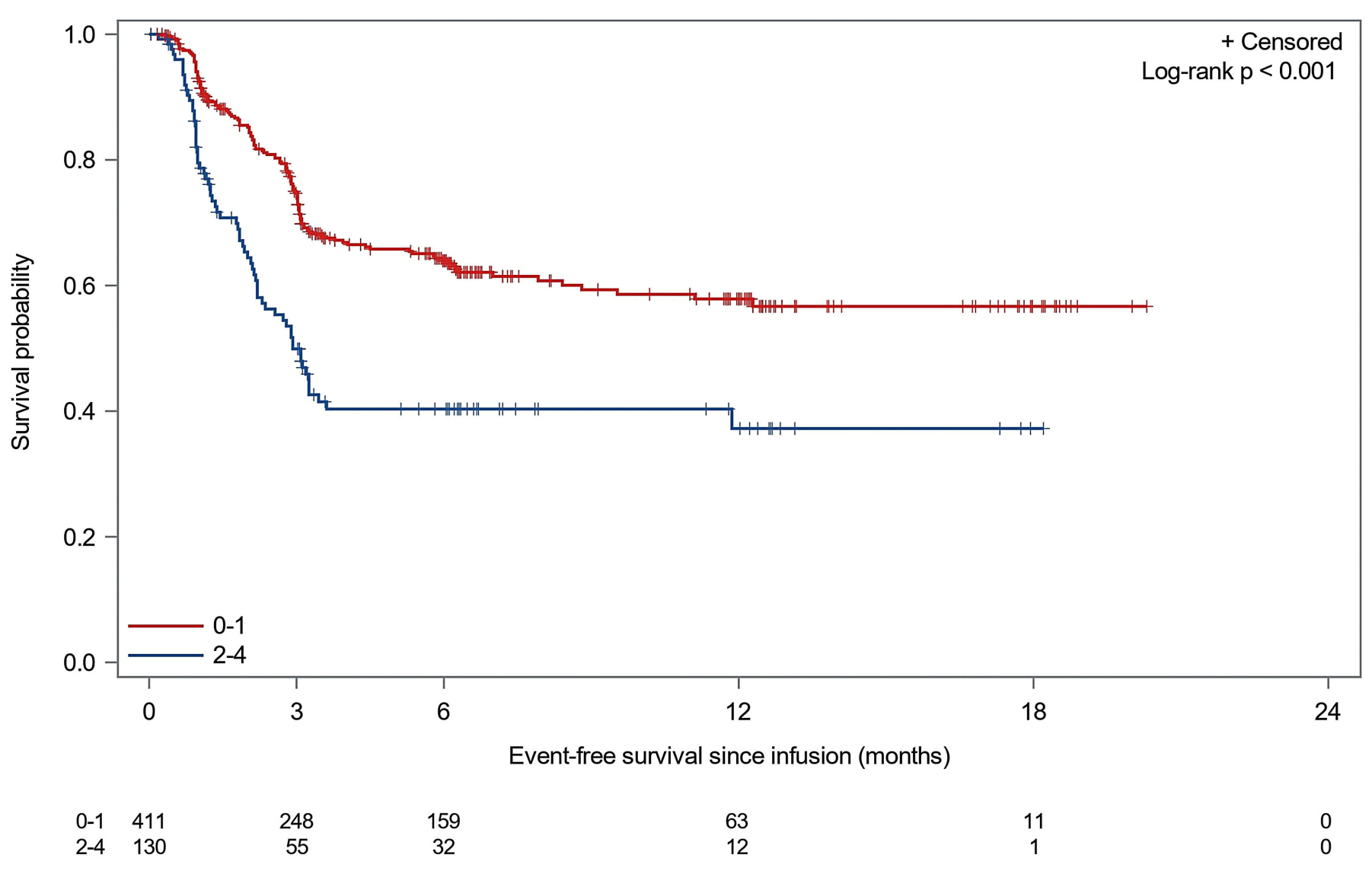
High	324	178	106	43	8	0
Low	145	72	48	12	0	

F



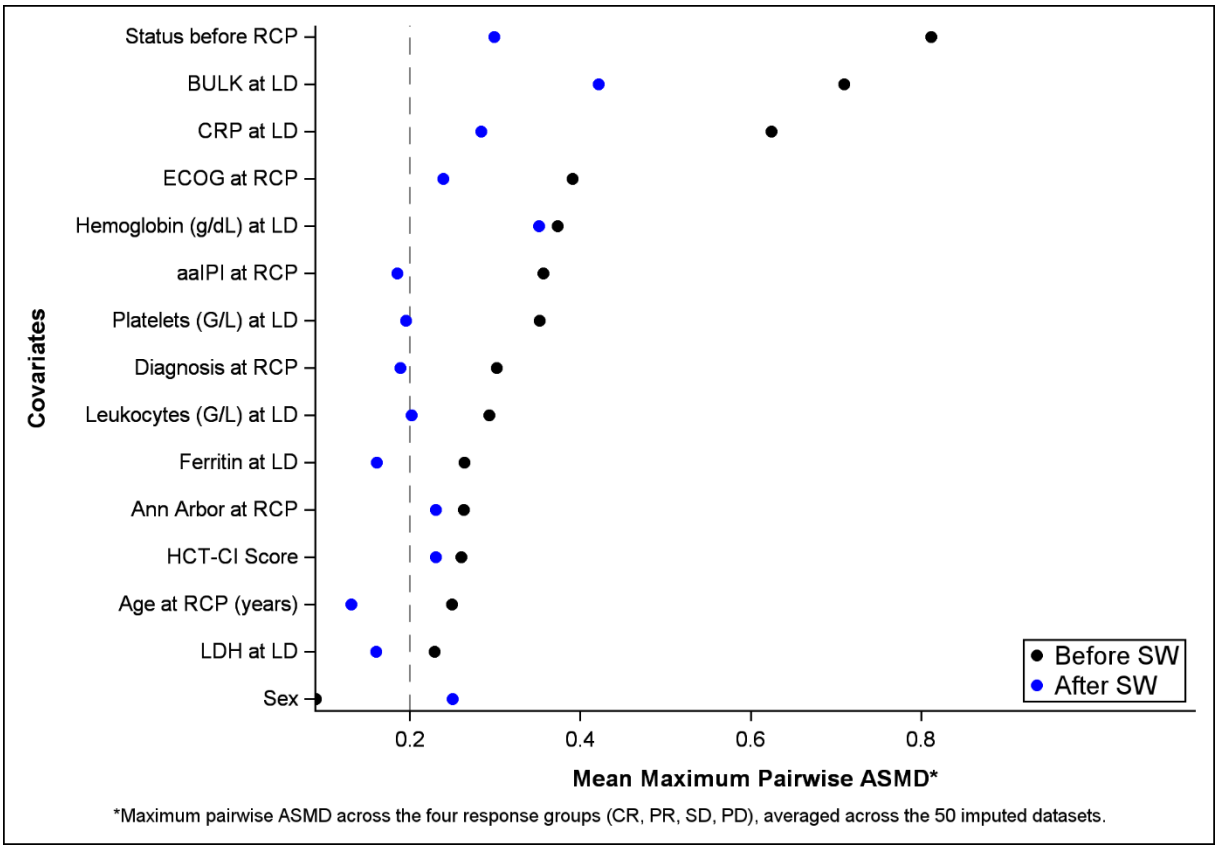
High	324	231	154	58	9	0
Low	145	103	69	19	2	0


A
1.0
0.8
0.6
0.4
0.2
0.0
Survival probability
+ Censored
Log-rank p = 0.009
CR or PR
SD or PD
0 3 6 12 18 24
Event-free survival since infusion (months)
CR or PR 226 139 89 29 4 0
SD or PD 258 127 78 32 5 0
B
1.0
0.8
0.6
0.4
0.2
0.0
Survival probability
+ Censored
Log-rank p < 0.001
CR or PR
SD or PD
0 3 6 12 18 24
Overall survival since infusion (months)
CR or PR 226 171 117 39 5 0
SD or PD 258 174 119 42 7 0
C
EFS
Unmatched
HR=0.68
(95%CI 0.50-0.91)
p-value=0.0084
Propensity score matched
HR=0.86
(95%CI 0.70-1.07)
p-value=0.1739
0.5
1
1.5
Lower risk of progression following axi-cel for responders vs non-responders
OS
HR=0.47
(95%CI 0.30-0.74)
p-value=0.0006
HR=0.70
(95%CI 0.51-0.96)
p-value=0.0292
0
0.5
1
1.5
Lower risk of progression following axi-cel for responders vs non-responders


+ Censored
Log-rank p < 0.001
Survival probability
1.0
0.8
0.6
0.4
0.2
0.0
0-1
2-4
0
3
6
12
18
24
Event-free survival since infusion (months)
0-1 411 248 159 63 11 0
2-4 130 55 32 12 1 0

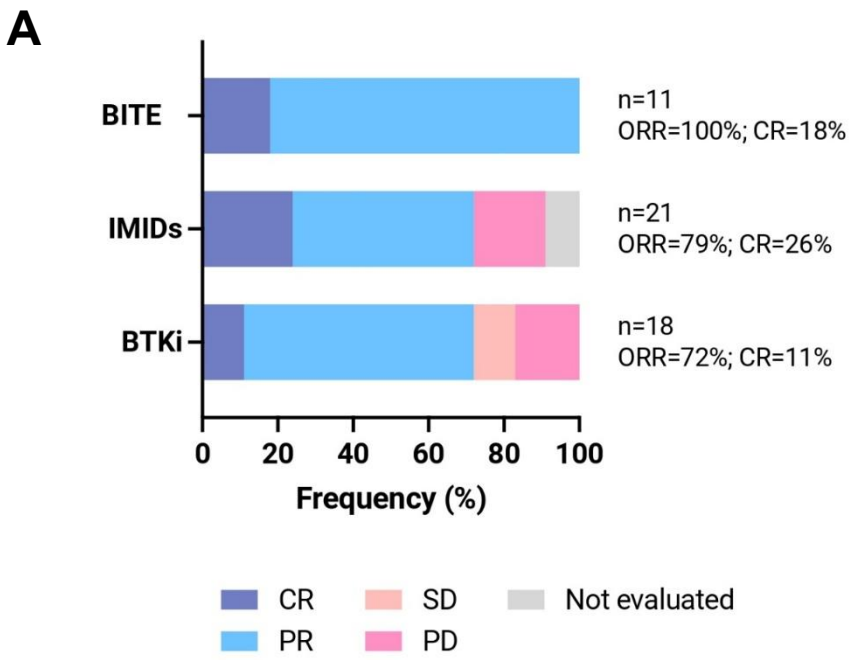
SUPPLEMENTARY FIGURES

Supplementary Figure 1. Covariate balance before and after propensity score weighting across H/BT response groups.



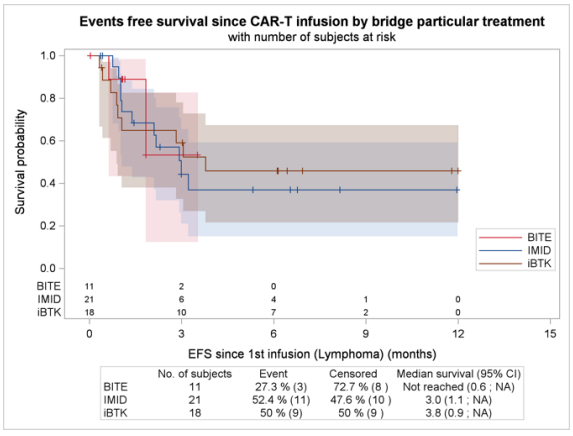
Maximum pairwise absolute standardized mean difference (ASMD) across H/BT response groups (CR, PR, SD, PD) for each covariate, before and after propensity score weighting, averaged across 50 imputed datasets. Dashed line indicates the balance threshold of 0.20.

Supplementary Figure 2. Response rates (A) one-year EFS (B) and OS (C) of patients receiving single agent T-cell engagers, immunomodulatory drugs or Bruton tyrosine kinase inhibitors as holding/bridging therapy.

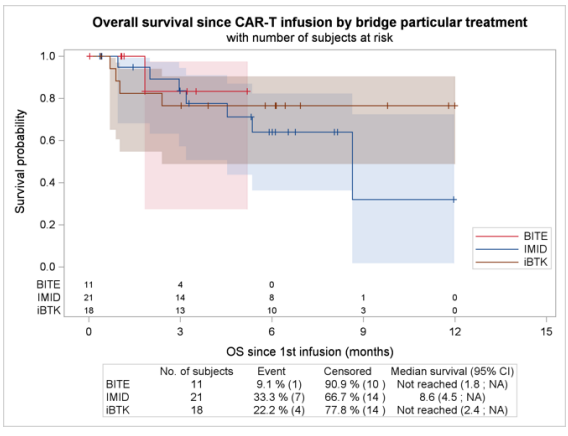


CR: complete response rate, PD: progressive disease, PR: partial response, SD: stable disease, ORR: overall response rate.

B



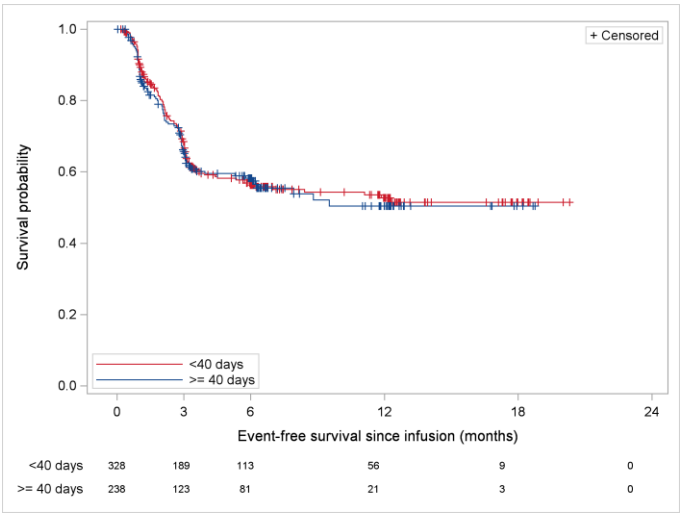
C



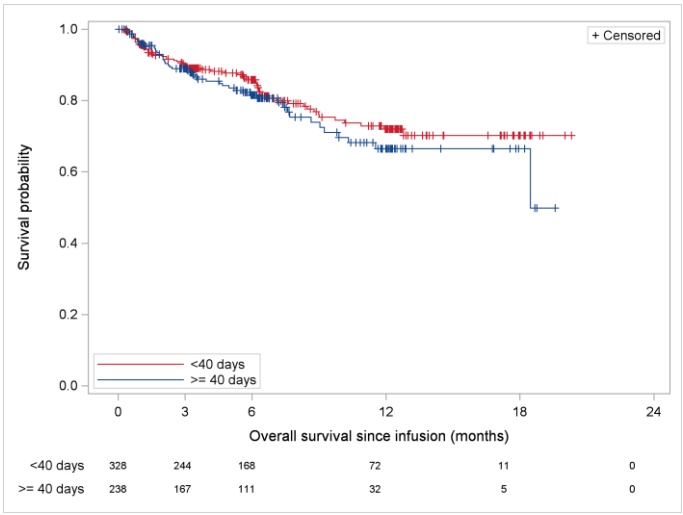
Supplementary Figure 3. Unmatched comparisons of EFS (A) and OS (B) according to H/BT response status.

Supplementary Figure 4. Comparisons of EFS (A) and (OS) according to vein-to-vein time.

A



B



SUPPLEMENTARY TABLES

Supplementary Table 1. List of covariates used for propensity score matching.

Covariates
Age at CAR-T eligibility (years)
LDH at lymphodepletion
Ferritin at lymphodepletion
aaIPI at CAR-T eligibility
Diagnosis at CAR-T eligibility
Platelets (G/L) at lymphodepletion
Leukocytes (G/L) at lymphodepletion
HCT-CI Score
Ann Arbor at CAR-T eligibility
ECOG at CAR-T eligibility
Sex
CRP at lymphodepletion
Status at CAR-T eligibility
Hemoglobin (g/dL) at lymphodepletion
Bulk at lymphodepletion

Supplementary Table 2. Maximum pairwise absolute standardized mean differences (ASMD) across the four responses to H/BT groups (CR, PR, SD, PD), averaged across the 50 imputed datasets.

Pairwise imputed ASMD*	Unweighted	Weighted
Age at RCP (years)	0.249	0.131
LDH at LD	0.229	0.161
Ferritin at LD	0.264	0.161
aaIPI at RCP	0.357	0.185
Diagnosis at RCP	0.302	0.189
Platelets (G/L) at LD	0.353	0.196
Leukocytes (G/L) at LD	0.293	0.202
HCT-CI Score	0.260	0.230
Ann Arbor at RCP	0.263	0.231
ECOG at RCP	0.391	0.239
Sex	0.090	0.250
CRP at LD	0.624	0.284
Status before RCP	0.812	0.299
Hemoglobin (g/dL) at LD	0.373	0.352
BULK at LD	0.709	0.422

* Absolute standardized mean differences

Supplementary Table 3. Patient characteristics according to their infusion status.

	Treated set		Test
	No N=69	Yes N=566	
Sex			Chi-2 P = 0.461
Male	47 (68.1%)	360 (63.6%)	
Female	22 (31.9%)	206 (36.4%)	
Age at RCP (years)			Wilcoxon P = 0.231
N	69	566	
Missing	0	0	
Mean (SD)	60.7 (13.25)	58.8 (13.31)	
Median	63.0	61.0	
Q1 ; Q3	54 ; 71	52 ; 69	
Min ; Max	25 ; 80	18 ; 82	
Age at RCP by class			Chi-2 P = 0.229
No	36 (52.2%)	338 (59.7%)	
Yes	33 (47.8%)	228 (40.3%)	
ECOG at RCP			Chi-2 P = 0.010
0-1	47 (79.7%)	449 (90.5%)	
>=2	12 (20.3%)	47 (9.5%)	
Missing	10	70	
aaIPI at RCP (in class)			Chi-2 P = 0.163
0-1	17 (32.1%)	190 (42.0%)	
2-3	36 (67.9%)	262 (58.0%)	
Missing	16	114	
High LDH at RCP*			Chi-2 P = 0.285
No	22 (32.8%)	220 (39.6%)	
Yes	45 (67.2%)	336 (60.4%)	
Missing	2	10	
HCT-CI score in class			Chi-2 P = 0.479
Low	39 (56.5%)	362 (64.0%)	
Intermediate	16 (23.2%)	107 (18.9%)	
High	14 (20.3%)	97 (17.1%)	
Ann Arbor Stage at RCP (in class)			Chi-2 P = 0.648
I-II	11 (18.6%)	84 (16.3%)	
III-IV	48 (81.4%)	431 (83.7%)	
Missing	10	51	
Status before RCP			Chi-2 P = 0.072
Refractory	57 (85.1%)	421 (75.2%)	
Relapse	10 (14.9%)	139 (24.8%)	
Missing	2	6	
Diagnosis at RCP (derived)			Fisher Exact P = 0.821
DLBCL	53 (76.8%)	442 (78.1%)	
PMBL	1 (1.4%)	17 (3.0%)	
HGBL	3 (4.3%)	30 (5.3%)	
Transformed indolent	11 (15.9%)	71 (12.5%)	
Other	1 (1.4%)	6 (1.1%)	
Prior autologous transplant			Fisher Exact P = 0.340
No	67 (97.1%)	557 (98.4%)	
Yes	2 (2.9%)	9 (1.6%)	
Bulky disease at lymphodepletion (>5cm)			Fisher Exact P = 1.000
No	3 (75.0%)	428 (79.1%)	
Yes	1 (25.0%)	113 (20.9%)	
Missing	0	24	
Bridging/Holding Status			Fisher Exact P = <0.001
No bridge	24 (34.8%)	52 (9.2%)	
Holding	7 (10.1%)	76 (13.4%)	
Bridging	27 (39.1%)	398 (70.3%)	
Holding/Bridging	11 (15.9%)	40 (7.1%)	
Response before CAR-T			Fisher Exact P = <0.001
Complete Response	3 (7.0%)	74 (14.5%)	
Partial Response	5 (11.6%)	152 (29.9%)	

	Treated set		Test
	No N=69	Yes N=566	
Stable Disease	1 (2.3%)	59 (11.6%)	
Progressive Disease	22 (51.2%)	199 (39.1%)	
Not Evaluated	12 (27.9%)	25 (4.9%)	
Missing	26	57	

Supplementary Table 4. H/BT distribution and number of lines.

	No bridge	Holding	Bridging	Holding/Bridging	Total
	N=52 (9%)	N=76 (13%)	N=398 (70%)	N=40 (7%)	N=566
Number of Holding treatments lines					
1	-	73 (96%)	-	37 (93%)	110 (95%)
2	-	3 (4%)	-	3 (7%)	6 (5%)
Number of Bridging treatments lines					
1	-	-	362 (91%)	36 (90%)	398 (91%)
2	-	-	30 (8%)	4 (10%)	34 (8%)
3	-	-	6 (1%)	0 (0%)	6 (1%)

Supplementary Table 5. Holding/bridging therapies' modalities.

STUDY COHORT		566			
H/BT		**514 (91%)**			
		Holding	**Bridging**	**Holding and Bridging**	**Overall**
		76 (15%)	398 (77%)	40 (8%)	514
CHEMOTHERAPY					**469 (91%)**
	Chemotherapy alone	63	325	24	412
	Chemotherapy + IMID	2	8	8	18
	Chemotherapy + BTKi	2	13	1	16
	Chemotherapy + BsAb	1	5	5	11
	Chemotherapy + IMID + BTKi	0	6	0	6
	Chemotherapy + BsAb + IMID	0	0	1	1
	Chemotherapy + BsAb + BTKi	0	1	0	1
	Chemotherapy + IMID + BCL2i	0	1	0	1
	Chemotherapy + anti-PD1	0	3	0	3
RADIATION THERAPY					**30 (6%)**
	Radiation therapy alone	3	27	0	30
TARGETED THERAPY					**11 (2%)**
	IMID	1	2	0	3
	BTKi	0	2	0	2
	IMID + BTKi	4	1	1	6
STEROIDS					**4 (1%)**
	Steroids alone	0	4	0	4
NO H/BT		**52 (9%)**			

BCL2i: BCL-2 inhibitor (venetoclax); BsAb: bispecific antibody anti-CD3xCD20; BTKi: Bruton tyrosine kinase inhibitor (ibrutinib); IMID: immunomodulatory imide drug (lenalidomide)

Supplementary Table 6. Classification of H/BT chemotherapy regimens.

CHEMO-BASED H/B THERAPY					
		Holding	**Bridging**	**Holding and Bridging**	**Overall**
		68 (15%)	362 (77%)	39 (8%)	469
By regimen type					
	Nucleoside analog	44	228	31	303 (65%)
	Cytarabine-based†	36	199	23	258 (85%)
	Gemcitabine-based†	8	29	8	45 (15%)
	Alkylating agent	24	117	6	147 (31%)
	Ifosfamide-based†	20	117	5	142 (97%)
	Other†	4	0	1	5 (3%)
	Anthracycline	0	13	2	15 (3%)
	Other	0	4	0	4 (<1%)
By intensity type					
	Low	19	113	13	145 (31%)
	High	49	249	26	324 (69%)

†Percentage given on each chemotherapy regimen cohort.

Supplementary Table 7. Description of the different H/BT chemotherapy regimens.

CHEMOTHERAPY			COMPOSITION	INTENSITY
Nucleoside analog				
	Cytarabine-based			
		DHAOx	Dexamethasone, Cytarabine, Oxaliplatin	High
	Gemcitabine-based			
		GemOx	Gemcitabine, Oxaliplatin	Low
		GVD	Gemcitabine, Vinorelbine, Doxorubicin	Low
Alkylating agent				
	Ifosfamide-based			
		ICE	Ifosfamide, Carboplatin, Etoposide	High
		Ifo/VP16	Ifosfamide, Etoposide	Low
	Other			
		Carmustine		Low
		Procarbazine		Low
Anthracycline				
	CHOP		Cyclophosphamide, Doxorubicine, Vincristine, Prednisone	High
	MIV		Mitoxantrone, Ifosfamide, Etoposide	High
Other				
	Platinum			Low
	Vinca-alkaloid			Low
	Methotrexate			Low

Supplementary Table 8. Patient characteristics according to intensity of chemotherapy received.

	Chemotherapy intensity		Test
	Low N=145	High N=324	
Sex			Chi-2 P = 0.915
Male	91 (62.8%)	205 (63.3%)	
Female	54 (37.2%)	119 (36.7%)	
Age at RCP (years)			Wilcoxon P = <0.001
N	145	324	
Missing	0	0	
Mean (SD)	62.9 (12.25)	57.6 (12.86)	
Median	67.0	60.0	
Q1 ; Q3	58 ; 71	50 ; 67	
Min ; Max	25 ; 81	18 ; 80	
ECOG at RCP			Chi-2 P = 0.958
0-1	116 (89.9%)	254 (89.8%)	
>=2	13 (10.1%)	29 (10.2%)	
Missing	16	41	
aaIPI at RCP (in class)			Chi-2 P = 0.313
0-1	50 (42.4%)	96 (36.9%)	
2-3	68 (57.6%)	164 (63.1%)	
Missing	27	64	
High LDH at RCP*			Chi-2 P = 0.066
No	60 (42.3%)	106 (33.3%)	
Yes	82 (57.7%)	212 (66.7%)	
Missing	3	6	
HCT-CI score in class			Chi-2 P = 0.630
Low	86 (59.3%)	207 (63.9%)	
Intermediate	30 (20.7%)	61 (18.8%)	
High	29 (20.0%)	56 (17.3%)	
Ann Arbor Stage at RCP (in class)			Chi-2 P = 0.729
I-II	18 (13.1%)	42 (14.4%)	
III-IV	119 (86.9%)	250 (85.6%)	
Missing	8	32	
Status before RCP			Chi-2 P = 0.397
Refractory	104 (72.7%)	246 (76.4%)	
Relapse	39 (27.3%)	76 (23.6%)	
Missing	2	2	
Diagnosis at RCP (derived)			Fisher Exact P = 0.394
DLBCL	112 (77.2%)	259 (79.9%)	
PMBL	2 (1.4%)	10 (3.1%)	
HGBL	11 (7.6%)	14 (4.3%)	
Transformed indolent	18 (12.4%)	39 (12.0%)	
Other	2 (1.4%)	2 (0.6%)	
Prior autologous transplant			Fisher Exact P = 0.260
No	141 (97.2%)	320 (98.8%)	
Yes	4 (2.8%)	4 (1.2%)	
Bulky disease at lymphodepletion (>5cm)			Fisher Exact P = 0.111
No	110 (82.1%)	234 (75.0%)	
Yes	24 (17.9%)	78 (25.0%)	
Missing	11	12	

Supplementary Table 9. Immunotherapies and targeted molecules for holding/bridging therapies, alone or in combination with chemotherapy.

H/BT treated patients	514	Holding		Bridging	
		L1	L2+	L1	L2+
Lenalidomide	21 (4%)	5		14	2
Ibrutinib	18 (4%)	2	0	14	2
CD3xCD20 bispecific antibodies	11 (2%)	1	0	4	6

Supplementary Table 10. Response to holding/bridging therapies.

H/BT treated patients		**514**	
H/BT treated patients evaluated for response to H/BT		**484**	
Responders		**227**	**46·7%**
	Complete Response	74	15·3%
	Partial Response	152	31·4%
Non-responders		**258**	**53·3%**
	Stable Disease	59	12·2%
	Progressive Disease	199	41·1%

Supplementary Table 11. Response according to holding/bridging therapies.

	H/BT treatment type				Treated set
	Chemotherapy N=449	Corticosteroids N=4	Immunotherapy /Targeted therapy N=10	Radiotherapy N=21	N=484
Overall Response Rate (ORR)	206 (45·9%)	1 (25·0%)	6 (60·0%)	13 (61·9%)	226 (46·7%)
95% confidence interval	[41·2%; 50·6%]	[0·6%; 80·6%]	[26·2%; 87·8%]	[38·4%; 81·9%]	[42·2%; 51·3%]
Complete Response Rate (CRR)	66 (14·7%)	1 (25·0%)	2 (20·0%)	5 (23·8%)	74 (15·3%)
95% confidence interval	[11·6%; 18·3%]	[0·6%; 80·6%]	[2·5%; 55·6%]	[8·2%; 47·2%]	[12·2%; 18·8%]

Supplementary Table 12. Cox proportional hazards model of survivals since first infusion according to bridging group.

Factor	Modality	Reference	Hazard Ratio	95% Hazard Ratio Confidence Interval		Likelihood Ratio		
				Lower	Upper	Chi-Square	DF	Pr > Chi-Square
EFS[†]								
New Treatment Status by patient	H/BT CHEMO	No bridge or CHEMO-FREE H/BT	1.616	1.086	2.403	6.3	1	0.0120
OS[††]								
New Treatment Status by patient	H/BT CHEMO	No bridge or CHEMO-FREE H/BT	1.829	1.022	3.273	4.79	1	0.0286

[†]Model is performed on 566 patients (218 events and 348 censoring).
[††]Model is performed on 566 patients (107 events and 459 censoring).
Statistics are from unstratified Cox proportional hazards model with ties handled using Efron.

Supplementary Table 13. Cox proportional hazards model of survivals since first infusion according to chemotherapy regimen.

Factor	Modality	Reference	Hazard Ratio	95% Hazard Ratio Confidence Interval		Likelihood Ratio		
				Lower	Upper	Chi-Square	DF	Pr > Chi-Square
EFS†								
Treatment subtype	Nucleoside analog-based	Alkylating agent-based	1.186	0.859	1.638	1.1	1	0.2940
OS††								
Treatment subtype	Nucleoside analog-based	Alkylating agent-based	1.310	0.822	2.087	1.34	1	0.2469

†Model is performed on 450 patients (179 events and 271 censoring).
††Model is performed on 450 patients (92 events and 358 censoring).
Statistics are from unstratified Cox proportional hazards model with ties handled using Efron.

Supplementary Table 14. Cox proportional hazards model of survivals since first infusion according to response after last bridge/holding treatment.

Factor	Modality	Reference	Hazard Ratio	95% Hazard Ratio Confidence Interval		Likelihood Ratio		
				Lower	Upper	Chi-Square	DF	Pr > Chi-Square
EFS†								
Response after last bridge/holding treatment (class)	CR or PR	SD or PD	0.676	0.504	0.907	6.95	1	0.0084
OS††								
Response after last bridge/holding treatment (class)	CR or PR	SD or PD	0.472	0.302	0.736	11.81	1	0.0006

†Model is performed on 484 patients (185 events and 299 censoring).
††Model is performed on 484 patients (91 events and 393 censoring).
Statistics are from unstratified Cox proportional hazards model with ties handled using Efron.

Supplementary Table 15. Propensity score matching: Weighted hazard ratios for survival by H/BT response category.

EFS					OS			
Pairwise comparisons	HR	95% CI		Pvalue	HR	95% CI		P value
		Lower	Upper			Lower	Upper	
Complete response vs Partial response	0·94	0·69	1·30	0·7190	1·31	0·78	2·18	0·3020
Complete response vs Stable disease	1·01	0·71	1·45	0·9354	0·98	0·57	1·66	0·9304
Complete response vs Progression	0·72	0·53	0·99	0·0458	0·72	0·44	1·16	0·1742
Partial response vs Stable disease	1·08	0·79	1·46	0·6363	0·75	0·46	1·20	0·2291
Partial response vs Progression	0·77	0·61	0·97	0·0300	0·55	0·38	0·79	0·0015
Stable disease vs progression	0·71	0·54	0·95	0·0198	0·74	0·49	1·11	0·1393
CR/PR vs SD/PD	**0·86**	**0·70**	**1·07**	**0·1739**	**0·70**	**0·51**	**0·96**	**0·0292**

Supplementary Table 13. Multivariate model for EFS.

Label	Parameter Estimate	Standard Error	P-value	Hazard Ratio	95% Lower Confidence Limit for Hazard Ratio	95% Upper Confidence Limit for Hazard Ratio
Response after last bridge/holding treatment	0·2131	0·1564	0·1732	1·24	0·91	1·68
AAIPI >1[†]	0·3571	0·1855	0·0544	1·43	0·99	2·06
LDH elevated[††]	0·4323	0·1880	0·0219	1·54	1·07	2·23
CRP elevated[††]	0·5176	0·1874	0·0059	1·68	1·16	2·42

[†]At 2L decision, [††]At infusion

Supplementary Table 14. EFS hazards ratio for prognostic score.

Label	Hazard Ratio	95% Lower Confidence Limit for Hazard Ratio	95% Upper Confidence Limit for Hazard Ratio	HR category / HR min	HR score by parameter
Response after last bridge/holding treatment	1·24	0·91	1·68	1	1
AAIPI >1[†]	1·43	0·99	2·06	1·1548830892	1
LDH elevated[††]	1·54	1·07	2·23	1·2451052888	1
CRP elevated[††]	1·68	1·16	2·42	1·3560106916	1

[†]At 2L decision, [††]At infusion

Supplementary Table 15. Optimal cut-off for vein-to-vein time regarding survival outcomes.

Variable	Survival outcomes	Vein-to-vein time cutoff	2.5% quantile	97.5% quantile	p-value*
Time from first infusion	OS	44	34	58	0,166
Time from first infusion	EFS	57	33	66	0,609

Confidence intervals were estimated by 10,000 bootstrap resamples
*p-value approximated by Lausen 1992 method

Supplementary Table 16. CAR-T cells associated toxicities according to response to H/BT.

	Safety set N=555	
CRS		
Any	519	(94%)
Grade 1-2	493	(89%)
Grade ≥ 3	26	(5%)
Missing grade	0	(0%)
Neurotoxicity		
Any	264	(48%)
Grade 1-2	169	(31%)
Grade ≥ 3	94	(17%)
Missing grade	1	(<1%)

Supplementary Table 17. CAR-T cells associated toxicities according to response to H/BT.

	Response after last bridge/holding treatment (class)				Safety set	
	CR or PR		SD or PD			
	N=225		N=250		N=475	
CRS						
Any	206	(92%)	237	(95%)	443	(93%)
Grade 1-2	198	(88%)	223	(89%)	421	(89%)
Grade ≥ 3	8	(4%)	14	(6%)	22	(5%)
Missing grade	0	(0%)	0	(0%)	0	(0%)
Neurotoxicity						
Any	98	(44%)	132	(53%)	230	(48%)
Grade 1-2	62	(28%)	85	(34%)	147	(31%)
Grade ≥ 3	35	(16%)	47	(19%)	82	(17%)
Missing grade	1	(<1%)	0	(%)	1	(<1%)
Non-Relapse Mortality						
Alive	151	(67%)	142	(57%)	293	(62%)
NRM	9	(4%)	19	(8%)	28	(6%)
Progression or death of lymphoma	65	(29%)	89	(36%)	154	(32%)

Supplementary Methods

Propensity Score Estimation

Propensity scores were estimated using a generalized boosted multinomial model, implemented via the mnps() function of the twang R package, with response to H/BT (CR, PR, SD, PD) as the four-category dependent variable. This approach extends standard binary propensity score estimation to settings with more than two comparison groups, generating pairwise propensity scores and weights that balance covariates simultaneously across all four response categories.

The following covariates were included in the model (**Supplementary Table 1**): age at CAR-T eligibility, diagnosis at CAR-T eligibility (DLBCL vs. PMBL vs. HGBL vs. Transformed indolent vs. Other), Ann Arbor stage at CAR-T eligibility (I–II vs. III–IV), age-adjusted IPI (aaIPI) at CAR-T eligibility (0–1 vs. 2–3), ECOG performance status at CAR-T eligibility (0–1 vs. ≥2), disease status at CAR-T eligibility (relapsed vs. refractory), HCT-CI score (Low vs. Intermediate vs. High), sex (male vs. female), bulky disease at LD (yes vs. no, threshold >5 cm), and, measured at lymphodepletion (LD): LDH, ferritin, CRP, platelet count, leukocyte count, and hemoglobin.

The underlying boosting algorithm was fit with 5,000 regression trees, using a fixed random seed (seed = 123) to ensure reproducibility. The optimal number of iterations was selected independently for each pairwise group comparison using two stopping rules, es.mean and ks.mean, which respectively minimize the average absolute standardized effect size and the average Kolmogorov–Smirnov statistic across covariates. Weights corresponding to the average treatment effect (ATE) estimand were derived, so that the weighted pseudo-population reflects the covariate distribution across all four H/BT response groups combined, rather than that of a single reference group.

Missing data. Propensity scores were estimated separately within each of 50 datasets generated by multiple imputation based on fully conditional specification (10 iterations), assuming data were missing at random using regression and discriminant function methods for continuous and categorical variables respectively, generating 50 imputed datasets. A separate mnps() model was fit for each imputed dataset, and the resulting weights were derived accordingly.

Balance diagnostics. Covariate balance was assessed using the absolute standardized mean difference (ASMD) computed for each pairwise combination of the four H/BT response groups, within each imputed dataset. The maximum pairwise ASMD across all covariates and all group comparisons was computed per imputed dataset, then averaged across the 50 imputed datasets to summarize overall residual imbalance (**Supplementary Table 2**). The maximum pairwise ASMD, when computed within each multiply imputed dataset and then averaged across imputations, tends to yield higher values on average than would be observed from a single (non-imputed) dataset. A threshold of 0.2, rather than the conventional 0.1, was considered indicative of satisfactory covariate balance in this context. Overall covariate balance was considered satisfactory across all variables under this criterion.