Safety and efficacy of bridging radiation therapy prior to CD19 CAR T for non-Hodgkin lymphoma: a systematic review and meta-analysis

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Abstract

Bridging radiation therapy (BRT) is increasingly utilized prior to CD19-directed chimeric antigen receptor T cells (CART19) in patients with non-Hodgkin lymphoma (NHL). However, its impact on outcomes of CART19 therapy is not established. We conducted a systematic review and meta-analysis to estimate the safety and efficacy of BRT prior to CART19 therapy. A comprehensive search was performed in databases from inception to October 2024. We identified 18 studies encompassing 538 adult NHL patients who received BRT prior to commercial CART19. Random-effect models were applied to explore meta-analysis outcomes. Diffuse large B-cell lymphoma was the most common diagnosis (73%), and axicabtagene ciloleucel was the most utilized product (67%). Bulky disease was present in 37%. The median dose of BRT was 30 Gy delivered comprehensively to all sites of positron emission tomography-avid disease in 76% of cases. The overall response rate to CART19 was 78.9%. At 1 year, the progression-free survival was 54.6% while overall survival was 71.2%. All-grade cytokine release syndrome (CRS) developed in 80% of cases while all-grade immune effector cell-associated neurotoxicity syndrome (ICANS) occurred in 39.4%. The rate of grade 3/4 CRS was 3.6%, while that of grade 3/4 ICANS was 10.6%. Sensitivity analyses including studies with bulky disease and excluding studies with patients who also received systemic bridging therapy, demonstrated consistent results compared to the main study findings. Subgroup meta-regression showed similar results in studies that utilized BRT only compared to studies that utilized combined-modality treatment. In conclusion, this meta-analysis found that BRT use prior to CART19, whether as a standalone approach or in combination with systemic therapy, does not increase toxicity or compromise the efficacy of CART19 therapy in NHL. Furthermore, the use of BRT is associated with a low rate of CRS, even in patients with bulky disease.

Introduction

CD19-directed chimeric antigen receptor (CAR) T cells (CART19) have emerged as a powerful immunotherapy and are now established as a standard of care for several subtypes of non-Hodgkin lymphoma (NHL) in the relapsed or refractory setting.[1-4] However, despite impressive initial response rates, only 30-40% of patient sustain long-term remission.[5,6] Due to the aggressive nature of the disease, a significant subset of patients require bridging therapy in the period between lymphocyte collection and CART19 infusion which often takes several weeks.[7] Therefore, bridging therapy is commonly administered during this period to control disease progression, achieve potential cytoreduction, and provide symptom palliation.[8] There is currently not a standardized approach to bridging therapy, with options including corticosteroids, immunochemotherapy, radiation, or combined-modality treatment (CMT), which combines radiation and systemic bridging therapy. The choice of bridging therapy is essential since outcomes of patients with high tumor burden at the time of CART19 therapy are less favorable.[9,10] Moreover, several real-world studies have shown improved outcomes for NHL patients who respond to bridging therapy.[8,11,12]

Bridging radiation therapy (BRT) has been increasingly utilized in this context for NHL patients as a single modality or as a part of CMT.[13] BRT has been favored by some clinicians and centers for its effectiveness in chemoresistant disease, ability to achieve rapid tumor debulking, and practicality in clinical settings. Furthermore, preclinical studies have suggested an ability of radiation to enhance CART19 efficacy, particularly when delivered shortly before infusion.[14-18] However, current knowledge regarding the impact of BRT on the safety and efficacy of CART19 therapy in NHL patients is based primarily on small and heterogeneous retrospective studies. The use of BRT in these studies was not standardized, with varying practices across centers regarding optimal radiation doses and fractionation, delivery methods, treatment fields and timing, thereby limiting the ability to draw definitive conclusions on both safety and efficacy.

In this systematic review and meta-analysis, we therefore sought to evaluate the efficacy and safety of BRT in conjunction with CART19 therapy in the current clinical landscape.

Methods

Design and search strategy

A librarian performed comprehensive searches using the Ovid MEDLINE, Ovid EMBASE, and The Cochrane Library (Wiley) databases for articles published between inception and 16 October, 2024. The search strategies are provided in *Online Supplementary Table S1*.

To limit publication bias, there were no language, publication date or type restrictions. Conference abstracts were excluded. Studies were screened using Covidence software by two independent reviewers (MAlh and RI). Inclusion criteria were: (i) adult NHL patients; (ii) Use of Food and Drug Administration-approved CART19 products; (iii) studies included ≥5 patients; and (iv) BRT administered between leukapheresis and CART19 infusion. Full texts were reviewed by MAlh and RI for final inclusion.

This study followed PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines and was conducted in accordance with the ethical standards of the United States.[19] The protocol was prospectively registered with PROSPERO (CRD42023440654) and is included in the *Online Supplementary Materials*.

Data extraction

The data collected included all relevant clinical and treatment details. A tumor was defined as bulky when its diameter was ≥7.5 cm or when it had a median bulk ≥6.5 cm. CMT referred to systemic bridging therapy combined with BRT. BRT parameters collected included total dose, number of fractions, and whether radiation targeted all positron emission tomography (PET)-avid sites or selected lesions. Primary outcomes were efficacy and CART19-related toxicity rates. Cytokine release syndrome (CRS) was graded according to American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading,[20] except in three studies that utilized alternative grading systems.[21-23]

Quality assessment

The Joanna Brigg's Institute appraisal tool was applied to assess study bias (*Online Supplementary Table S2*).[24] Visual inspection of funnel plot asymmetry and Egger regression tests were used to assess reporting bias (*Online Supplementary Figure S1*).[25]

Statistical analysis

Data were analyzed in RStudio (v. 4.2.1), using the *meta* and *metafor* R packages. Endpoints for each study were calculated as proportion of events out of total number of patients by performing random-effect meta-analyses. Clopper-Pearson (exact) binomial interval was used for 95% confidence intervals (95% CI). The rates were transformed with the Freeman-Tukey Double arcsine transformation (PFT) method before pooling. An inverse variance weighting method with random effect was used for pooling the effect sizes. Forest plots were used to visualize results.

Restricted maximum-likelihood estimation was used to estimate the heterogeneity variance τ^2. The Q-profile method was used to calculate the confidence interval of τ^2. The between-study heterogeneity was assessed by the variance τ^2, as well as I^2 statistics. Heterogeneity was assessed using Cochran's Q test and quantified using I^2, with I^2 values of <40%, 30-60%, 50-90%, and 75-100% reflecting low, moderate, substantial, and considerable heterogeneity, respectively. Small-study effect was assessed by funnel

plots and Egger's test. Studies with missing values were removed from analysis for that outcome.

Sensitivity analyses

Meta-analyses were repeated after: (i) testing fixed-effect models; (ii) excluding studies with CMT; (iii) excluding studies without bulky disease; and (iv) excluding studies with potential overlap of patients.[26]

Meta-regression analysis

A meta-regression analysis was performed to compare individual outcomes between studies that used BRT and studies that used CMT as a bridging strategy. The meta-regression was calculated based on mixed-effect models accounting for both within-study and between-study heterogeneity.

Results

Study cohort

We screened 1,072 studies for reports on safety and efficacy of BRT in NHL patients before receiving CART19 therapy. Overall, 67 full-text articles were assessed, of which 18 articles encompassed a total of 538 patients fulfilling the criteria for downstream analysis (Figure 1).[8,21,22,27-41] Overall, diffuse large B-cell lymphoma was the most common histology (391 patients, 73%), followed by transformed follicular lymphoma (55 patients, 10%), primary mediasti-

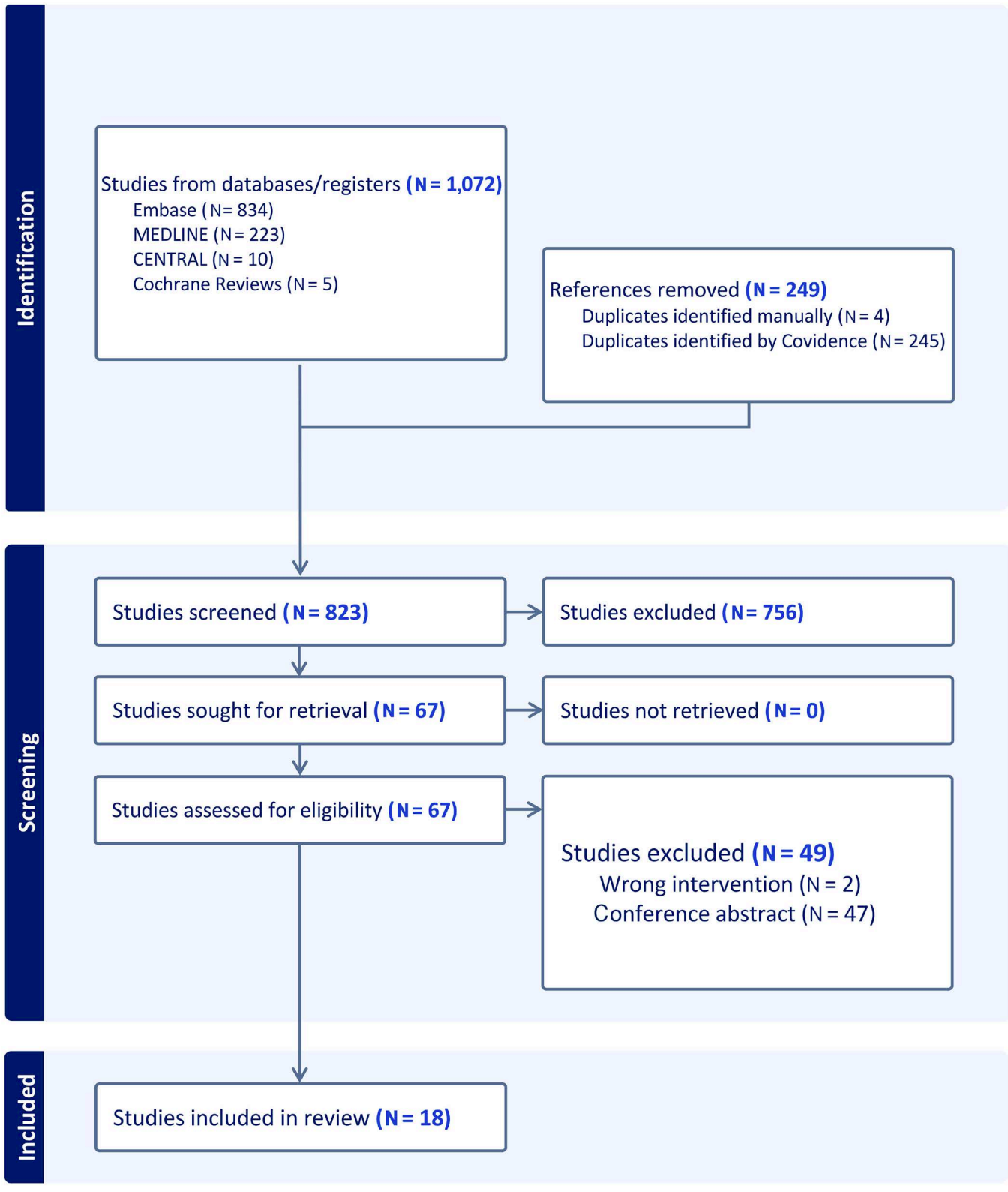

Figure 1. Flowchart of the systematic review according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) 2020 flow diagram.

nal B-cell lymphoma (19 patients, 4%), high-grade B-cell lymphoma (14 patients, 3%), and mantle cell lymphoma (11 patients, 2%). Among the studies that specified the type of CART19 product used,[21,22,27-30,33-38,40,41] axicabtagene ciloleucel (axi-cel) was the most commonly utilized (67%) followed by tisagenlecleucel (tisa-cel; 24%), lisocabtagene maraleucel (liso-cel; 6%), and brexucabtagene autoleucel (brexu-cel; 2%). Approximately half of the patients at the time of BRT had advanced stage B-cell NHL (Ann Arbor stage III/IV; 48%), and 28% had an International Prognostic Index of ≥3. The median number of lines of therapy received prior to CART19 was two and 37% of patients had bulky disease prior to BRT, defined as a tumor diameter ≥7.5 cm or a median tumor bulk diameter ≥6.5 cm. The median total radiation dose delivered was 30 Gy (range, 2-54) over a median of ten fractions (range, 5-15). Most patients (76%) were treated with comprehensive BRT to all sites of PET-avid disease. CMT was administered to 10% of the total cohort. The full characteristics of the studies included are provided in Table 1.

Efficacy of CART19 following bridging radiation therapy

Across all studies, the pooled overall response rate to CART19 was 78.9% (95% CI: 69.9-86.9%) (Figure 2). At 1 year, the estimated pooled progression-free survival (PFS) was 54.6% (95% CI: 45.0-64.1%), while pooled overall survival (OS) at 1 year was 71.2% (95% CI: 63.1-78.8%) (Figure 2).

Toxicity of CART19 following bridging radiation therapy

We evaluated three CART19-related toxicities in the total cohort: CRS, immune effector cell-associated neurotoxicity syndrome (ICANS), and persistent severe cytopenia, defined as grade 3/4 neutropenia, anemia, or thrombocytopenia, according to the Common Terminology Criteria for Adverse Events (CTCAE v5), which persists for at least 90 days following CART19 infusion.

The pooled estimate of all-grade CRS was 80% (95% CI: 63-93.1%), while the pooled estimate of all-grade ICANS was 39.4% (95% CI: 18.3-62.6%) (*Online Supplementary Figure S2*). The pooled estimate of severe CRS (grade 3/4) was 3.6% (95% CI: 1.5-6.3%), while the pooled estimate of severe ICANS (grade 3/4) was 10.6% (95% CI: 4.0-19.3%) (Figure 3). Of the 18 studies included in the meta-analysis, only five provided data on persistent grade 3/4 cytopenia.[8,22,27,36,39] Three studies reported multilineage cytopenia, including neutropenia, anemia and thrombocytopenia.[22,27,36] One study reported both neutropenia and thrombocytopenia,[8] while another study reported thrombocytopenia alone.[39] Among those studies, the pooled estimate of grade 3/4 neutropenia was 12.6% (95% CI: 0-39.1%), the pooled estimate of grade 3/4 anemia was 14.2% (95% CI: 3.3-29.3%), and the pooled estimate of grade 3/4 thrombocytopenia was 8.8% (95% CI: 0.08-21.7%) (*Online Supplementary Figure S3*).

Sensitivity analyses

We conducted multiple sensitivity analyses to validate the robustness of primary results of the total cohort. Notably, the fixed-effect model yielded results consistent with the main study findings, reinforcing their robustness (Table 2). Furthermore, we performed an additional sensitivity analysis, excluding studies that included patients bridged with CMT (Table 1), to specifically evaluate the outcomes of BRT alone.[8,21,28-30,35,38-41] While we observed a slight increase in all-grade CRS and all-grade ICANS, with pooled rates of 93.1% (95% CI: 77.9-100%) and 50.2% (95% CI: 13.4-86.9%), respectively, the efficacy rates, as well as grade 3/4 CRS and ICANS remained stable (Table 2).

Given that radiation has historically been utilized as a cytoreductive tool for patients with bulky disease who tend to respond less favorably to CART19 therapy,[9,10] we aimed to evaluate the role of BRT in this subgroup. For this sensitivity analysis, we included only studies in which ≥30% of patients had bulky disease[8,22,27,30,31,33,37,39] (Table 1), as previously defined. While the pooled overall response rate was slightly higher at 84.7% (95% CI: 73.5-93.5%) compared to that of the total cohort, and the pooled OS rate at 1 year was slightly lower at 66.8% (95% CI: 60.2-73.1%), the pooled PFS rate at 1 year remained stable at 55.6% (95% CI: 48.2-62.9%). Notably, the rates of CART19-related toxicities, particularly pooled grade 3/4 CRS and ICANS, were lower than the rates in the overall study cohort. The pooled rate of severe CRS was 2.3% (95% CI: 0-6.5%), while the pooled rate of severe ICANS was 8.9% (95% CI: 1.7-19.6%) (Table 2). Lastly, to eliminate duplication bias, in addition to excluding studies that reported the same patient population and selecting the one with longer follow-up period, we conducted a sensitivity analysis excluding studies from the same center, even when the accrual period differed, retaining only the study with the larger number of patients for analysis. For this sensitivity analysis, three studies were excluded;[8,31,32] efficacy and safety results remained consistent with the findings of the main study (Table 2).

Meta-regression analysis

To strengthen the findings of our sensitivity analysis, which demonstrated comparable CART19 efficacy and safety outcomes in studies that used BRT only and the total cohort, we performed a subgroup meta-regression analysis. This analysis compared CART19 outcomes between studies that used BRT only[8,21,28-30,35,38-41] to outcomes in studies that involved patients who received CMT (BRT combined with bridging systemic therapy)[22,27,31-34,36,37] (Table 1). Efficacy outcomes were comparable between the BRT and CMT groups, with no statistically significant differences in overall response rate (P=0.85), PFS (P=0.67), or OS (P=0.83) (*Online Supplementary Figure S4*). Similarly, CART19-related toxicities were consistent across groups showing no significant differences in all-grade CRS (P=0.13) or ICANS (P=0.95) (*Online Supplementary Figure S5*), as well as in grade 3/4 CRS (P=0.89) and ICANS (P=0.70) (Figure 4).

Table 1. Patients and disease-specific baseline characteristics.

Study's author N of patients total=538	CART19 product, %	Age, years, median (range); Gender, %; ECOG PS, %	Histology, %; Stage, %; IPI, %	Bulky disease >7.5cm, %	LOT prior to CART19, median (range); Prior ASCT, %	Systemic therapy during bridging, %	Total radiation dose, Gy, median, (range); Fraction per course, median (range)	Radiation regimen (focal *vs.* comp)*	Response to BRT
Hubbeling *et al.* N=32	Axicel: 46 Tisacel: 25 Lisocel: 22 Brexucel: 7	66 (22-85) M: 73 F: 27 NA	DLBCL: 78 MCL: 19 BL: 3 I/II: 27 III/IV: 73 NA	46	3 (2-8) 20%	41	30 Gy (4-54) 10 (2-30)	Comp: 39% Focal: 61%	In-field ORR: 84%, Progression outside BRT field: 56%
Ladbury *et al.* N=12	Axicel: 100	65 (21-75) M: 41.7 F: 58.3 PS2-3: 25	DLBCL: 91.7 tFL: 8.3 III/IV: 58.3 IPI ≥3: 16.7	16.7	2 (2-5) NA	0	20 Gy (4–40) NA	Comp: 66.7 Focal: 33.3	NA
Lutfi *et al.* N=14	Axicel: 100	55.5 M: 28.6 F: 71.4 PS0: 35.7 PS1: 64.3	DLBCL: 78.6 PMBCL: 7.1 tFL: 14.3 I/II: 64.3 III/IV: 35.7 IPI 0-1: 35.7 IPI 2: 42.9	28.6	2 (1-5) NA	0	NA	NA	NA
Pinnix *et al.* N=11	Axicel: 100	68 (51-84) M: 82 F: 18 PS2-3: 9	DLBCL: 100 I/II: 18 III/IV: 82 IPI ≥3: 55	Defined as >10 cm: 36	2 (2-3) NA	0	35.2 Gy (10-45)	Comp: 64 Focal: 36	NA
Roddie *et al.* N=54	Axicel Tisacel[#]	57 (49-65) M: 61.1 F: 38.9 PS0: 53.7 PS1: 46.3	DLBCL: 63 PMBCL: 7.4 tFL: 25.9 t-Other: 3.7 I/II: 30.2 III/IV: 69.8 Unknown: 1 IPI 0-2: 55.1 IPI ≥ 3: 44.9	37	27.8 received >2 16.7	0	NA	NA	NA

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Study's author N of patients total=538	CART19 product, %	Age, years, median (range); Gender, %; ECOG PS, %	Histology, %; Stage, %; IPI, %	Bulky disease >7.5cm, %	LOT prior to CART19, median (range); Prior ASCT, %	Systemic therapy during bridging, %	Total radiation dose, Gy, median, (range); Fraction per course, median (range)	Radiation regimen (focal *vs.* comp)*	Response to BRT
Saifi *et al.* (A) N=34	Axicel Tisacel Brexucel Lisocel#	59 (19-73) M: 57.1 F: 42.9 NA	DLBCL: 62.9 FL: 5.7 HGBCL: 11.4 MCL: 2.9 NA	Median bulk diameter 8.7 cm	NA	15	23.3 Gy (4-48)	NA	NA
Saifi *et al.* (B) N=14	Axicel Tisacel Brexucel#	50 (24-72) M: 42.9 F: 57.1 NA	DLBCL: 85.7 tDLBCL: 7.1 HGBCL: 7.1 NA	NA	2 (1-5) NA	7.1	20 Gy (15-36) 5 (3-24)	NA	NA
Sim *et al.* N=11	Axicel: 100	NA	DLBCL: 73 tFL: 27 I/II: 36 III: 18 III/IV: 45 IPI 1: 9 IPI 2: 36 IPI 3: 36 IPI 4: 9 IPI 5: 9	Defined as >10 cm: 67	3 (1-5) NA	64	20 Gy (6-30) 5 (3-10)	NA	NA
Wright *et al.* N=5	Tisacel: 60 Axicel: 40	NA	DLBCL: 84 tFL: 13 PMBCL: 3 II: 19 III: 16 IV: 65 NA	Defined as >10 cm: 40	NA	40	37.5 Gy (20-45) 15 (5-20)	Comp: 60 Focal: 40	NA

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Study's author N of patients total=538	CART19 product, %	Age, years, median (range); Gender, %; ECOG PS, %	Histology, %; Stage, %; IPI, %	Bulky disease >7.5cm, %	LOT prior to CART19, median (range); Prior ASCT, %	Systemic therapy during bridging, %	Total radiation dose, Gy, median, (range); Fraction per course, median (range)	Radiation regimen (focal *vs.* comp)*	Response to BRT
Fan *et al.* N=20	Tisacel: 90 $10^{\#}$	54.5 (35.8, 61.2) M: 65 F: 35 NA	DLBCL 100 I: 10 II: 15 III: 10 IV: 65 IPI 0: 5 IPI 1: 15 IPI 2: 30 IPI 3: 35 IPI 4: 15	16.7	35 received ≥4 NA	25	36 Gy (8-50)	NA	NA
van Meerten *et al.* N=14	Axicel: 100	NA	NA	NA	NA	0	NA	NA	NA
Jain *et al.* N=19	Axicel: 100	NA	DLBCL: 100	NA	NA	0	30 Gy (20-30.6) 10 (5-10)	Focal: 31.5 Unknown: 69.5	NA
Manzar *et al.* N=51	Axicel: 78.4 Tisacel: 3.9 Lisocel: 17.7	65 (24-87) M: 70.6 F: 29.4 PS0: 9.8 PS1: 64.7 PS2: 19.6 PS3: 5.9	DLBCL: 78.4 tFL: 13.7 PMBCL: 7.8 I/II: 35.3 III/IV: 64.7 IPI 1: 11.8 IPI 2: 27.5 IPI 3: 37.3 IPI 4: 13.7 IPI 5: 9.8	25.5	51 received ≥3 9.8	31.4	30 Gy (4-48) 10 (2-23)	Comp: 61 Focal: 40	NA
Saifi *et al.* (C) N=48	Axicel: 81.3 Brexucel: 8.3 Tisacel: 6.2 Lisocel: 4.2	60 (19-84) M: 54.2 F: 45.8 NA	DLBCL: 62.5 FL: 6.3 HGBCL: 18.8 MCL: 8.3 PMBCL: 4.2 NA	Median tumor size 6.8 cm, range (1.7-21)	2 (1-4) NA	10.4	25.5 Gy (9.3-43)	Comp: 77 Focal: 23	NA

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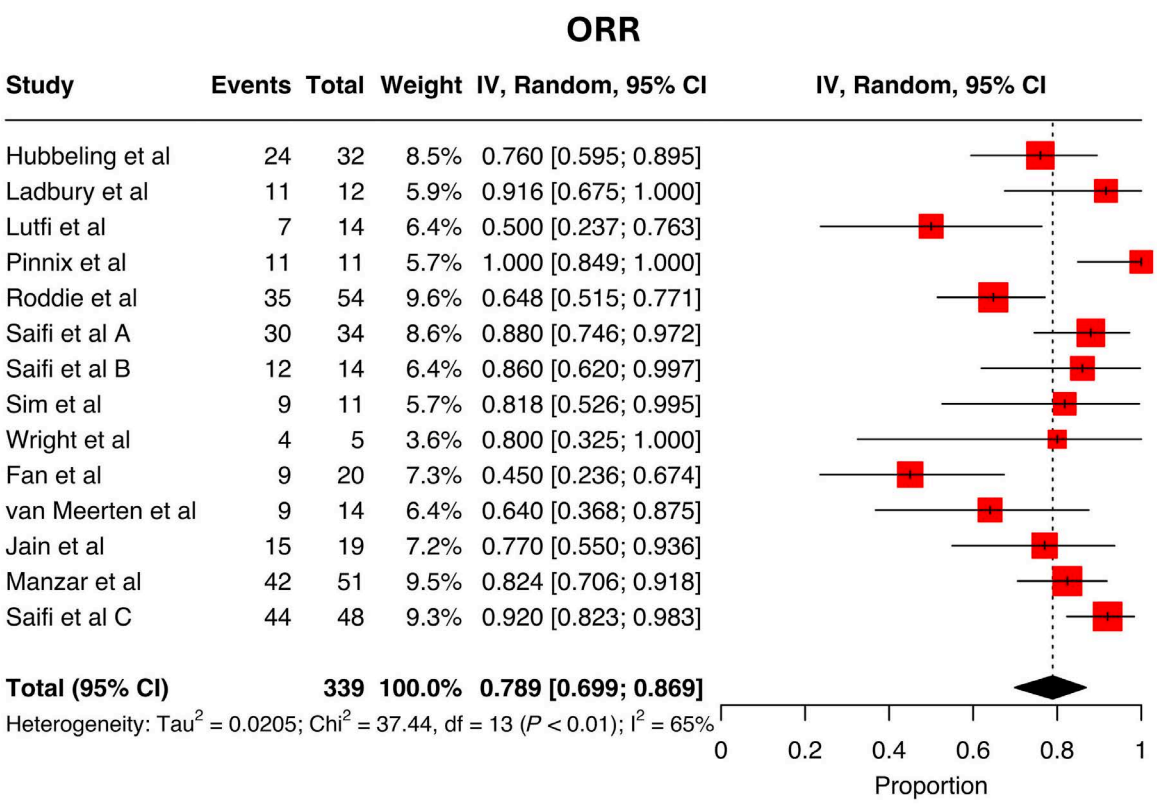
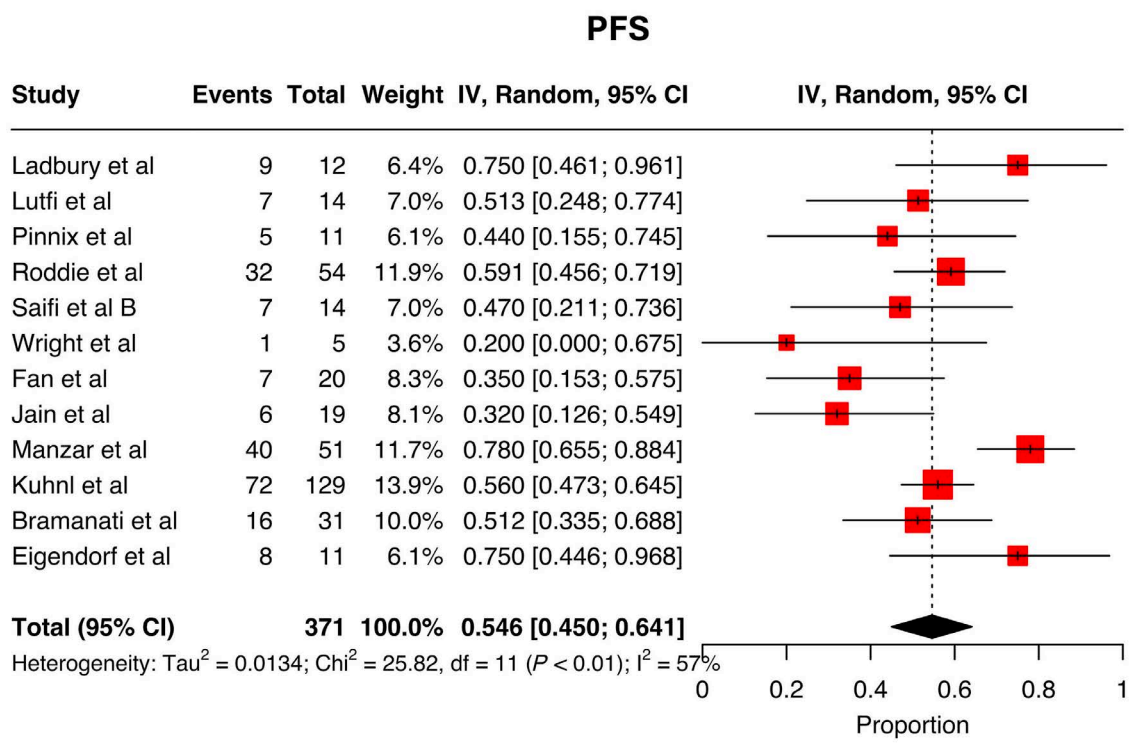
Study's author N of patients total=538	CART19 product, %	Age, years, median (range); Gender, %; ECOG PS, %	Histology, %; Stage, %; IPI, %	Bulky disease >7.5cm, %	LOT prior to CART19, median (range); Prior ASCT, %	Systemic therapy during bridging, %	Total radiation dose, Gy, median, (range); Fraction per course, median (range)	Radiation regimen (focal *vs.* comp)*	Response to BRT
Ababneh *et al.* N=28	Axicel: 64.3 Tisacel: 35.7	68.5 (21-82) M: 71.4 F: 28.6 PS0-1: 71.4 PS2-4: 28.6	DLBCL: 50 FL: 35.7 HGBCL: 7.1 PMBCL: 3.6 U-BCL: 3.6 I/II: 35.7 III/IV: 64.3 IPI ≥3: 64.3 IPI <3: 35.7	Defined as ≥5 cm: 58.3	NA 17.9	0	NA	NA	NA
Kuhnl *et al.* N=129	Axicel Tisacel[#]	60 M: 62.8 F: 37.2 PS0: 55.2 PS1: 44.8	60 M: 62.8 F: 37.2 PS0: 55.2 PS1: 44.8	34.5	27.9 received >2 17.8	0	30 Gy (2-39)	NA	NA
Bramanti *et al.* N=31	Axicel: 37.2 Tisacel: 62.8	57 (21-70) M: 67.7 F: 32.3 PS0: 80.6 PS1: 19.4	DLBCL: 93.5 tDLBCL: 6.5 I: 3.2 II: 22.6 III: 12.9 IV: 61.3 NA	NA	2:64.5 3:25.8 4:3.2 ≥5:6.5 38.7	0	Mean: 28 Gy (17.5-36) Mean: 11 (5-20)	Comp: 48 Focal: 52	NA
Eigendorff *et al.* N=11	Tisacel: 100	63 (50-73) M: 55 F: 45 NA	DLBCL: 100 NA	Defined as ≥5 cm: 64	55 received ≥3 27	0	NA	NA	ORR: 45%

*Radiotherapy is considered "comprehensive" if it treats all sites of positron emission tomography (PET)-avid (or regions suspicious for) lymphoma. Radiotherapy is considered focal if it treats just some areas of PET avidity. Generally, focal irradiation is used for areas requiring palliation or for perceived higher-risk lesions (bulky, extranodal, etc.). #Subgroup percentage not provided. CART19: CD19-directed chimeric antigen receptor (CAR) T cells; ECOG PS: Eastern Cooperative Oncology Group performance status; IPI: International Prognostic Index; LOT: line of therapy; ASCT: autologous stem cell transplantation; comp: comprehensive; BRT: bridging radiation therapy; axicel: axicabtagene ciloleucel; tisacel: tisagenlecleucel; lisocel: lisocabtagene maraleucel; brexucel: brexucabtagene autoleucel; M: male; F: female; NA: not available; DLBCL: diffuse large B-cell lymphoma; MCL: mantle cell lymphoma; BL: Burkitt lymphoma; ORR: overall response rate; tFL: transformed follicular lymphoma; PMBCL: primary mediastinal B-cell lymphoma; t-Other: other transformed lymphomas; HGBCL: high-grade B-cell lymphoma; U-BCL: unclassifiable B-cell lymphoma.





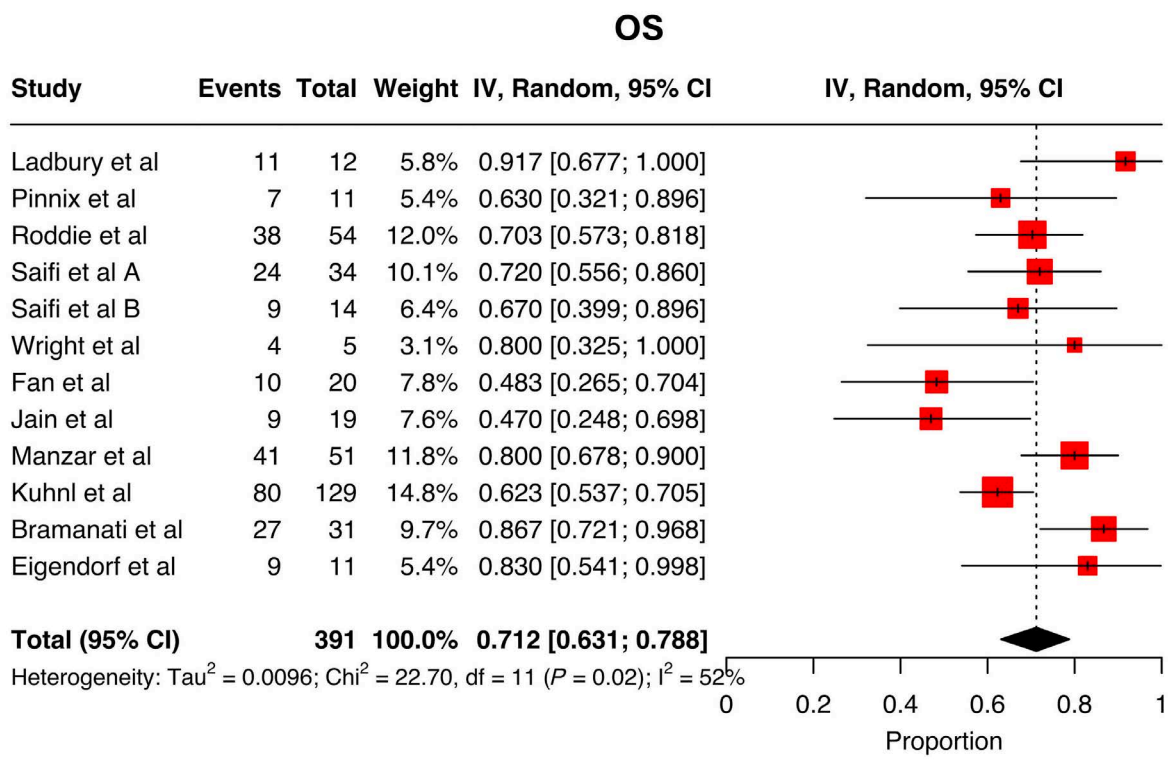


Figure 2. Forest plots of overall response rate, progression-free survival and overall survival among patients from the studies included in the meta-analysis. ORR: overall response rate; 95% CI: 95% confidence interval; IV: inverse variance; PFS: progression-free survival; OS: overall survival.

Discussion

BRT has emerged as a widely utilized strategy in the context of CART19 therapy in B-cell NHL, owing to its feasibility, the radiosensitive nature of the diseases, and the accessibility of radiation facilities in tertiary care centers. Early adoption of BRT was supported by anecdotes of strong and rapid cytoreductive power particularly for chemorefractory states.[30] While numerous data have subsequently emerged, current supporting evidence mostly comes from small, heterogeneous retrospective studies, with no prospective data available to date. Initial concerns about using radiation in this context centered on its safety and the potential to exacerbate CART19-related toxicities by propagating inflammation. Additional concerns included the hypothetical negative impact of radiation on CART19 efficacy through two potential mechanisms: (i) the risk that the cytoreductive effect of radiation might reduce tumor antigens, potentially limiting CAR T-cell expansion, and (ii) the risk of CART19 exhaustion due to an enhanced immune response triggered by radiation. To our knowledge, this is the first meta-analysis evaluating the role of BRT prior to CART19 therapy in NHL patients. Our findings demonstrate that BRT, whether administered alone or in combination with systemic bridging therapy, does not increase toxicity or compromise the efficacy of CART19 therapy in NHL.

Our efficacy results are promising considering that patients who require bridging usually manifest adverse risk features

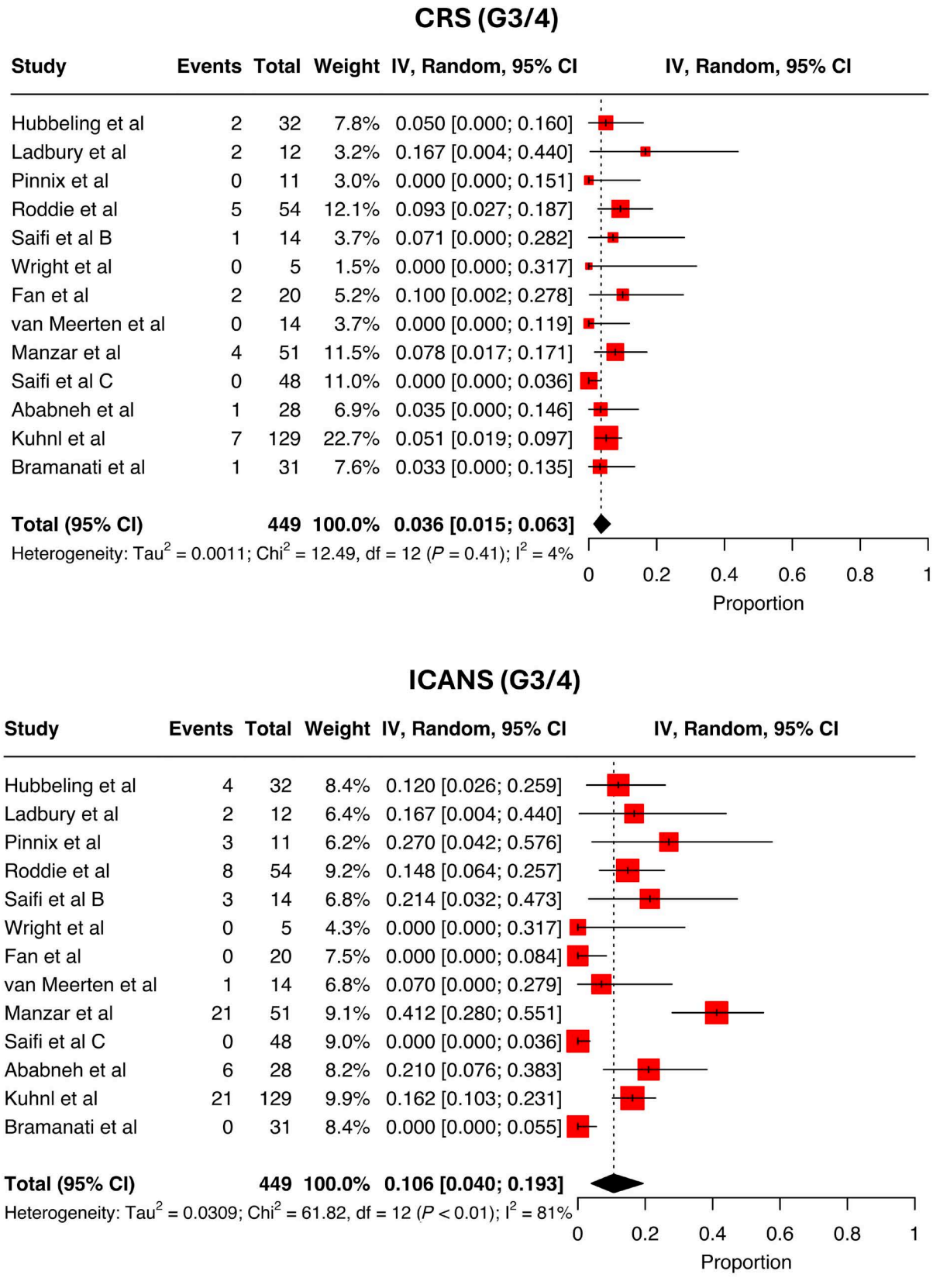


Figure 3. Forest plots of grade 3/4 cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome among patients from the studies included in the meta-analysis. CRS (G3/4): cytokine release syndrome grade 3 or 4; 95% CI: 95% confidence interval; IV: inverse variance; ICANS (G3/4): immune effector cell-associated neurotoxicity syndrome grade 3 or 4.

with higher tumor burden. Among the total cohort, 91% received axi-cel or tisa-cel and diffuse large B-cell lymphoma was the most common entity. Registrational CART19 trials reported 1-year PFS and OS rates of 44.5% and 59% for axi-cel, respectively, and 33% and 49% for tisa-cel in the setting of relapsed/refractory large B-cell lymphoma.[3,5] We observed improved outcomes, with 1-year PFS at 54.6% and OS at 71.2%. These results underscore the potential benefit of tumor cytoreduction achieved through BRT. This finding is consistent with our recent report demonstrating that effective bridging therapy, particularly for NHL patients with a high metabolic tumor burden, is associated with improved CART19 outcomes.[12] Furthermore, these results align with the growing body of preclinical evidence demonstrating the positive impact of radiation on the efficacy of CAR T cells through several mechanisms. Our group, along with others, has demonstrated that low-dose radiation administered prior to CAR T-cell therapy enhances the cells' cytotoxicity and expansion, intra-tumoral trafficking, and longevity in both *in vitro* and *in vivo* settings.[14-17] These benefits are driven by enhanced antigen presentation on tumor cells, upregulation of death signaling pathways which improve T-cell antigen-independent killing, and enhanced lymphodepletion.[17] Additionally, recent preclinical evidence suggests that local radiation can prime a systemic CAR T-cell response, suggesting an abscopal effect.[18]

Importantly, our results indicate a low rate of grade 3/4 CRS when BRT is used prior to CART19 therapy. In pivotal CART19 trials, grade 3/4 CRS rates were reported to be 13% and 23% for axi-cel and tisa-cel, respectively, in the setting of relapsed/refractory large B-cell lymphoma,[3,42] and 6% and 5% in the second-line setting,[1,43] which closely mirrors real-world evidence.[44] In contrast, we observed a relatively lower rate of grade 3/4 CRS of 3.6% across the total cohort. Our sensitivity analysis demonstrated that this low grade 3/4 CRS rate remained consistent, even with studies that enrolled a significant proportion of patients with bulky disease (Table 2). Similarly, we found 10.6% grade 3/4 ICANS, which is lower than the rates reported with axi-cel (21% in the second-line setting[1] and 28% in the relapsed/refractory setting), and comparable to rates reported with tisa-cel.[3] One explanation could be that the successful cytoreduction achieved through radiation therapy results in a lower tumor burden, which may subsequently reduce the risk of CRS.[12] Another potential explanation involves the immunomodulatory effects of radiation therapy. While radiation stimulates the immune system through various mechanisms, it also activates compensatory pathways that result in immunosuppression.[45] One such pathway is the activation of stimulator of interferon genes (STING), which triggers non-canonical NF-κB signaling in dendritic cells. This, in turn, leads to immunosuppression by decreasing the expression of type I interferons.[46]

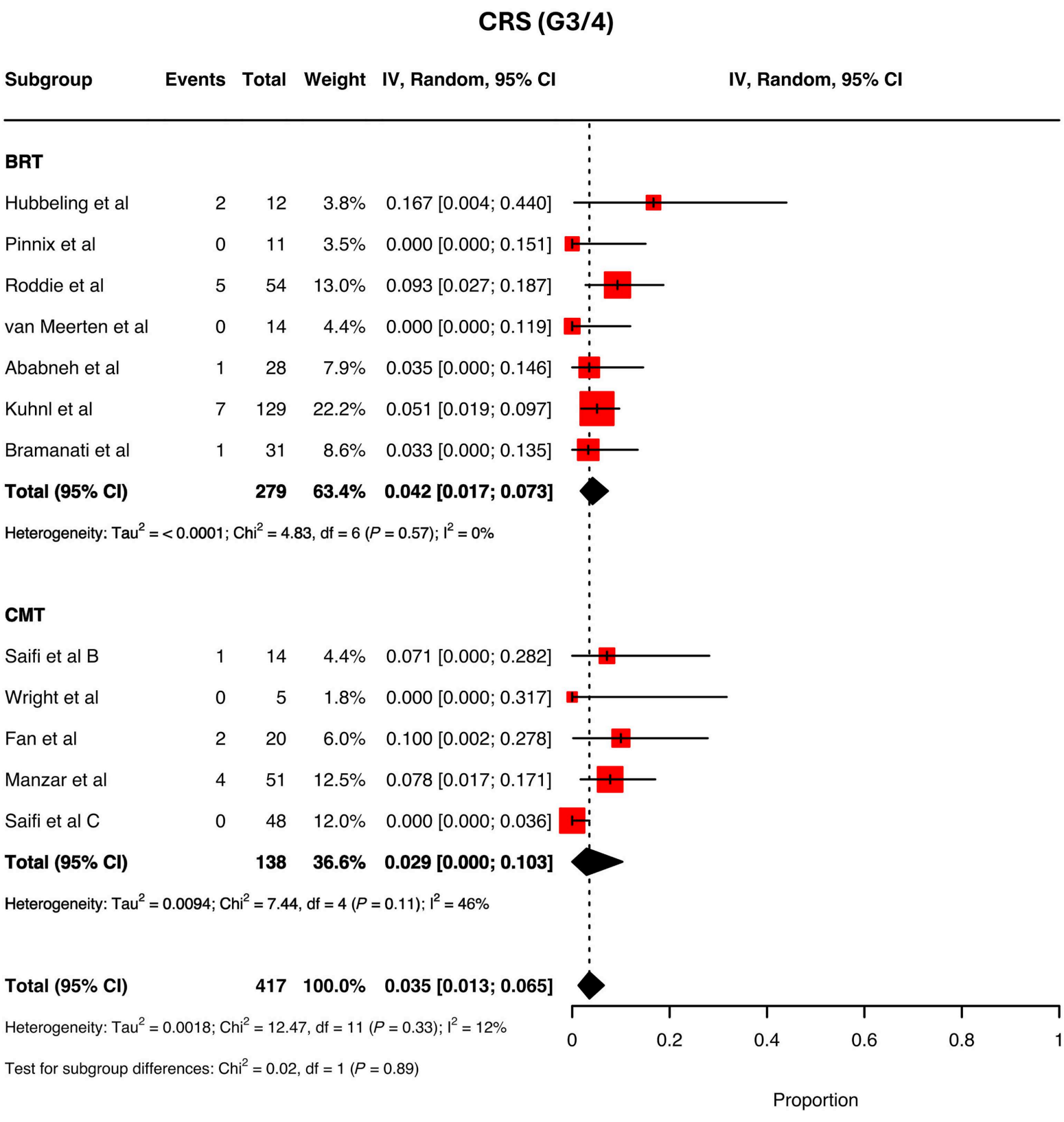
Our findings highlight a significant gap and unmet need for quality reporting on the use of BRT in the context of CART19 therapy. Notably, among the 18 studies analyzed, none stratified outcomes by B-cell NHL subtype, and only one study has differentiated BRT outcomes based on the CART19 product used, signaling increased toxicity with axi-cel compared to tisa-cel.[40] This limitation precluded our ability to analyze outcomes by CART19 products or disease subtypes. Moreover, we observed a lack of reporting on key aspects such as the use of BRT in second-line *versus* later-line settings, the response to BRT prior to CART19

Table 2. Results of sensitivity analyses comparing reported main results using random-effect models.

Results	Reported results: Random-effects model including all studies	Sensitivity analysis 1: Fixed-effects model including all studies	Sensitivity analysis 2: Random-effects model excluding studies with systemic bridging therapy	Sensitivity analysis 3: Random-effects model excluding studies with <30% bulky disease	Sensitivity analysis 4: Random-effects model excluding studies with potential overlap of patients
Efficacy, % (95% CI)					
Overall response rate	78.9 (69.9-86.9)	79.4 (74.6-83.9)	76.3 (59.1-90.3)	84.7 (73.5-93.5)	78.7 (67.3-88.5)
Progression-free survival	54.6 (45.0-64.1)	57 (51.7-62.3)	55.5 (49.4-61.5)	55.6 (48.2-62.9)	52.4 (39.9-64.6)
Overall survival	71.2 (63.9-78.5)	70 (65.4-74.9)	72 (60.2-82.5)	66.8 (60.2-73.1)	70.6 (57.7-82.2
Safety, % (95% CI)					
Cytokine release syndrome					
All-grades	80 (63.0-93.1)	74.8 (68.9-80.2)	93.1 (77.9-100)	74.3 (52.9-91.4)	80 (63-93.1)
Grades 3/4	3.6 (1.5-6.3)	3.6 (1.7-5.9)	4.2 (1.7-7.3)	2.3 (0-6.5)	2.9 (0.09-5.6)
ICANS					
All-grades	39.4 (18.3-62.6)	34 (27.3-41.0)	50.2 (13.4-86.9)	26.6 (14.6-40.2)	39.4 (18.3-62.6)
Grades 3/4	10.6 (4.0-19.3)	11.6 (8.5-15.1)	12.2 (5.2-21.1)	8.9 (1.7-19.6)	9.5 (2.4-19.5)

Sensitivity analyses compared reported main results using a random-effects model to: 1. a fixed-effects model; 2. studies with only bridging radiation therapy and no combined-modality treatment; 3. studies with only bulky disease; 4. studies without potential patient overlap. 95% CI: 95% confidence interval; ICANS: immune effector cell-associated neurotoxicity syndrome.

infusion, comparisons of outcomes between patients who received BRT and those who either did not receive bridging therapy or underwent other strategies, the precise timing of BRT in relation to the start of lymphodepletion or CART19 infusion, and the documentation of radiation-specific acute and long-term adverse effects. Another critical area lacking attention is the hypothetical risk of increased hematotoxicity associated with BRT use, recently recognized as immune effector cell-associated hematotoxicity (ICAHT).[47] These gaps underscore the pressing need to conduct prospective studies to systematically evaluate and document BRT use in a standardized manner – particularly with respect to the timing, number of fractions, and total dose – to reduce heterogeneity and strengthen the validity of conclusions. Such efforts will ultimately facilitate the development of consensus guidelines for the use of BRT in the context of CART19 therapy. Of note, given the heterogeneity of patient and disease scenarios which present for consideration of bridging, it is unlikely that a single "BRT regimen" will be feasible and, instead, flexible guidance will need to be proposed. Investigating BRT prospectively will also enable the incorporation of correlative studies to further elucidate the effects of radiotherapy on CART19 mechanistically and its phenotypic composition. To address these concerns, our group, along with others, has initiated a prospective phase I study to evaluate the safety and efficacy of BRT in patients with large B-cell lymphoma undergoing CART19 therapy (NCT05574114). At present, we see several situations



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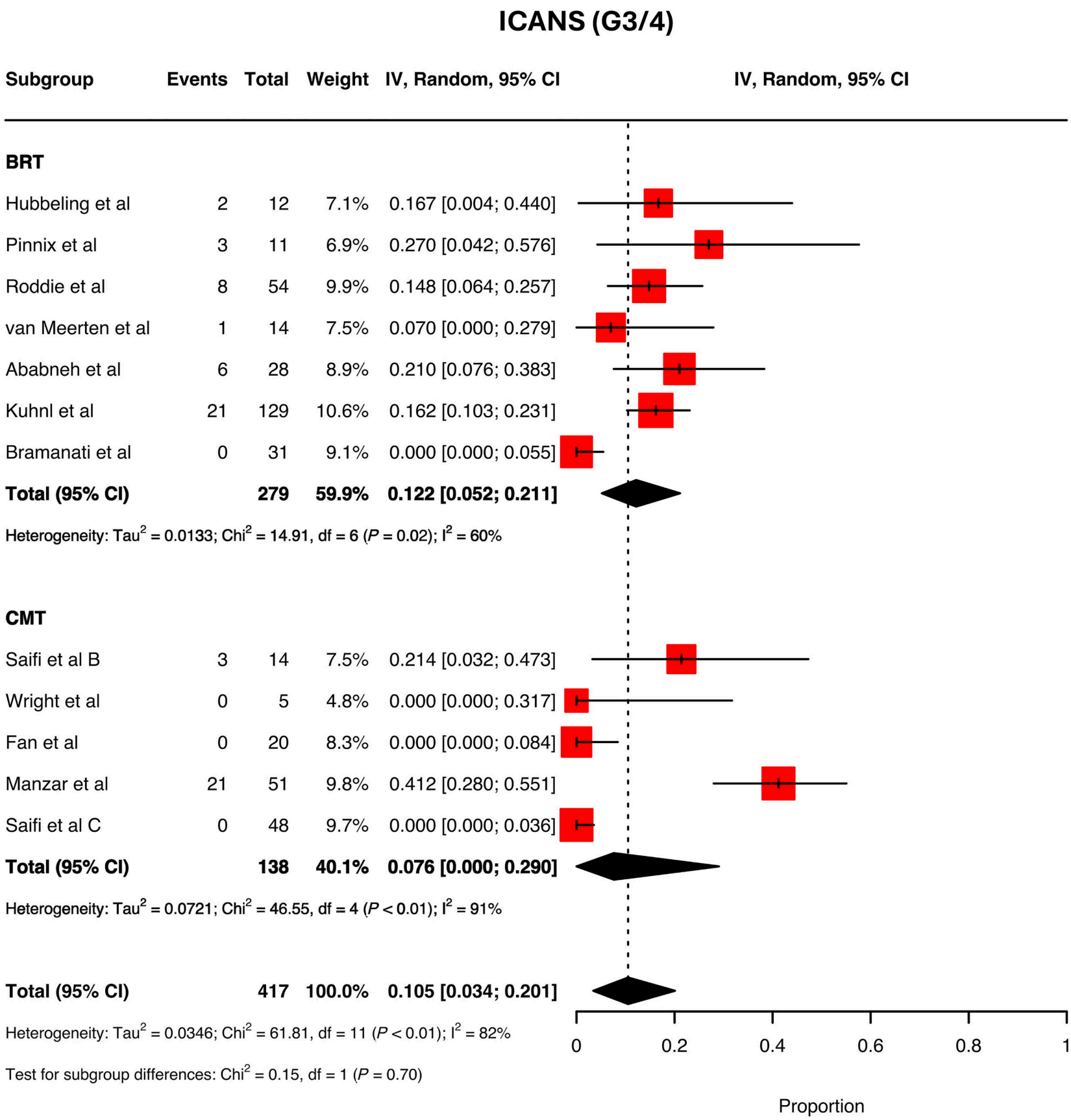

Figure 4. Meta-regression analysis comparing outcomes in bridging radiation therapy studies to outcomes in combined-modality treatment studies represented as forest plots including grade 3/4 cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome. CRS (G3/4): cytokine release syndrome grade 3 or 4; 95% CI: 95% confidence interval; IV: inverse variance; BRT: bridging radiation therapy; CMT: combined-modality treatment; ICANS (G3/4): immune effector cell-associated neurotoxicity syndrome grade 3 or 4.

in which BRT could benefit patients planned for CART19. Perhaps the most important is when patients have lesion(s) which are symptomatic, where BRT can offer rapid palliation. There are now ample data indicating that patients who have a significant burden of metabolically active disease are likely to have poorer post-CART19 outcomes and greater toxicity, and BRT has demonstrated power to induce rapid cytoreduction in patients. Importantly, patients in whom cytoreduction is successful appear to have similar outcomes to those with a low baseline burden of disease.[48] Thus, we feel that delivery of BRT to treat significant reservoirs of disease even in the context of advanced-stage disease is sensical. There is also growing utilization of BRT for lesions with a perceived likelihood of local relapse after CART19;

while these features warrant further study, characteristics such as bulk, high avidity and certain extranodal/anatomic sites are considered higher risk.[49] Other situations may become more standard in the future given promising preclinical data including using BRT to prime or augment a CART19 response, or overcome an immunosuppressive microenvironment;[50,51] these indications are highly exciting but there are limited clinical data at this time.

There are several limitations to our meta-analysis, including the lack of individual patient data, and heterogeneity among the included studies. We addressed this limitation by conducting multiple sensitivity analyses and incorporating both random-effect and fixed-effect models, all of which showed stability of our main study findings (Table 2). Furthermore, we found no evidence of publication bias based on funnel plot analysis and Egger's test (*Online Supplementary Figure S1*).

In conclusion, our meta-analysis found that the use of BRT prior to CART19, whether as a standalone approach or in combination with systemic bridging therapy, does not increase toxicity or compromise the efficacy of CART19 therapy in NHL. Furthermore, it is associated with a lower rate of CRS compared to the rate in historical controls, even in patients with bulky disease. Ultimately, these results highlight the importance of disease control at the time of CART19 infusion for subsequent toxicity and response and invite future prospective clinical trials incorporating BRT into innovative next-generation bridging concepts.

Disclosures

MS has served as a paid consultant for McKinsey & Company, Angiocrine Bioscience, Inc. and Omeros Corporation; has received research funding from Angiocrine Bioscience, Inc., Omeros Corporation, Amgen Inc., Bristol-Myers Squibb and Sanofi; has served on ad hoc advisory boards for Kite – A Gilead Company and Miltenyi Biotec; and has received honoraria from i3Health, Medscape, CancerNetwork, Intellisphere LLC and IDEOlogy. RS has received speaker's honoraria from Sanofi and Incyte. AG-A has served on ad hoc advisory boards for Kite – A Gilead Company and Sanofi.

Contributions

MAlh, RI and SY conceived and designed the study. MAlh, RI and MD performed the screening and selection for the study. MD provided administrative and technical support. MAlh and ZC performed the statistical analysis. MAlh, RI, BSI and SY wrote the original draft. KR, MS, RS, PP, MAlj, MLG, JY and KvB critically reviewed the manuscript for important intellectual content. MAlh, RI, KR, MS, RS, TT, JM, MF, AG-A, TS, PP, MLG, JY, KVB, BSI, ZC and SY edited and reviewed the manuscript. SY, ZC and BSI supervised the study.

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Data-sharing statement

Data used and/or analyzed in this article are original and are available from the corresponding author on reasonable request.

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