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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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Conflict of Interest

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Data Sharing:

Data used and/or analyzed during this submission are original and they are available from the corresponding author on reasonable request.

Abstract:

Bridging radiation therapy (BRT) is increasingly utilized prior to CART19 in NHL patients. However, its impact on CART19 outcomes 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 encompassed 538 adult NHL patients who received BRT prior to commercial CART19. Random-effect models were applied to explore meta-analysis outcomes. DLBCL was the most common diagnosis (73%), and axicabtagene ciloleucel was the most utilized product (67%). Bulky disease was present in 37%. Median BRT dose was 30 Gy delivered comprehensively to all sites of PET avid disease in 76% of cases. ORR to CART19 was 78.9%. At 1 year, PFS was 54.6% while OS was 71.2%. All-grade CRS was 80% while all-grade ICANS was 39.4%. Grade 3/4 CRS was 3.6% and 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. Sub-group 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, use of BRT is associated with 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 requires 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]. Currently, bridging therapy lacks a standardized approach, with options including corticosteroids, immunochemotherapy, radiation, or combined-modality treatment (CMT), which combines radiation and systemic bridging therapy. The bridging therapy choice 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 chemo-resistant 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 primarily based on small and heterogeneous retrospective studies. The use of BRT in these studies lacks standardization, 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 **Supplementary Table 1.**

To limit publication bias, there were no language, publication date or type restrictions. Conference abstracts were excluded. Studies were screened using Covidence software by 2 independent reviewers (MA and RI). Inclusion criteria required: 1. Adult NHL patients, 2. Use of FDA approved CART19 products, 3. Studies include ≥ 5 patients, 4. BRT administered between leukapheresis and CART19 infusion. Full texts were reviewed by MA and RI for final inclusion.

This study followed PRISMA guidelines and 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 **Supplementary Materials**.

Data Extraction: Data collection included all relevant clinical and treatment details. Bulky tumor was defined as diameter ≥7.5 cm or median bulk ≥6.5 cm. CMT referred to systemic bridging therapy combined with BRT. BRT parameters collected including total dose, number of fractions, and whether radiation targeted all PET avid sites or selected lesions. Primary outcomes were efficacy and CART19-related toxicity rates. Cytokine release syndrome (CRS) was graded according to 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 (**Supplementary Table 2**) [24]. Visual inspection of funnel plot asymmetry and Egger regression tests were used to assess reporting bias (**Supplementary Fig.1)** [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 interval (CI). The rates were transformed with Freeman-Tukey Double arcsine transformation (PFT) method before pooling. Inverse variance (V) weighting method with random effect was used for pooling the effect sizes. Forest plots were used to visualize results.

Restricted maximum-likelihood estimator (REML) was used to estimate the heterogeneity variance τ^2. Q-Profile method (QP) was used to calculate the CI of τ^2. The between-study heterogeneity was assessed by 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 plot and Egger's test. Studies with missing values were removed from analysis for that outcome.

Sensitivity analyses: Meta-analyses were repeated after 1. testing fixed-effect models, 2. Excluding studies with CMT, 3. excluding studies without bulky disease, and 4. Excluding studies with potential patient overlap [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 encompass 538 total patients fulfilling the criteria for downstream analysis (**Fig. 1**) [8,21,22,27-41].

Overall, diffuse large B-cell lymphoma (DLBCL) was the most common histology (391 patients, 73%), followed by transformed follicular lymphoma (55, 10%), primary mediastinal B-cell lymphoma (19, 4%), high-grade B-cell lymphoma (14, 3%), and mantle cell lymphoma (11, 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 patients at the time of BRT had advanced stage B-cell NHL (Ann Arbor stage III/IV; 48%), and 28% had international prognostic index of ≥ 3. The median number of lines of therapy received prior to CART19 was 2 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 10 fractions (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. Full characteristics of the included studies are provided in **Table 1**.

Efficacy of CART19 following BRT:

Across all studies, the pooled overall response rate (ORR) to CART19 was 78.9% (95% confidence interval (CI): 69.9 – 86.9%) (**Fig. 2**). At 1 year, 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%) (**Fig. 2**).

Toxicity of CART19 following BRT:

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), that persists for at least 90 days following CART19 infusion.

The pooled estimate of all-grade CRS was 80% (95% CI: 63 – 93.1%), while pooled estimate of all-grade ICANS was 39.4% (95% CI: 18.3 – 62.6%) (**Supplementary Fig. 2)**. 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%) (**Fig. 3**).

Of the 18 studies included in the meta-analysis, only 5 studies provided data on persistent grade 3/4 cytopenia [8,22,27,36,39]. Three studies reported multi-lineage 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%) (**Supplementary Fig. 3).**

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 where ≥30% of patients had bulky disease [8,22,27,30,31,33,37,39] **(Table 1)**, as previously defined. While the pooled ORR was slightly higher at 84.7% (95% CI: 73.5 – 93.5%) compared to 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, CART19 related toxicities, particularly pooled rates grade 3/4 CRS and ICANS were lower compared to the overall study cohort. Pooled severe CRS rate was 2.3% (95% CI: 0 – 6.5%), while 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 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 accrual period differed, retaining only the study with the larger patient sample for analysis. For this sensitivity analysis, three studies were excluded [8,31,32], efficacy and safety results remained consistent with the main study findings **(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 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 BRT and CMT groups, with no statistically significant differences in ORR (p=0.85), PFS (p=0.67), or OS (p=0.83) **(Supplementary Fig. 4)**. Similarly, CART19 related toxicities were consistent across groups showing no significant differences in all-grade CRS (p=0.13) or ICANS (p=0.95) **(Supplementary Fig. 5)**, as well as in grade 3/4 CRS (p=0.89) and ICANS (p=0.70) **(Fig. 4).**

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 largely 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 concern included the hypothetical negative impact of radiation on CART19 efficacy through two potential mechanisms: (1) the risk that the cytoreductive effect of radiation might reduce tumor antigens, potentially limiting CAR T-cell expansion, and (2) 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 patients who require bridging usually manifest adverse risk features with higher tumor burden. Among the total cohort, 91% received axi-cel or tisa-cel and DLBCL 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 relapsed/refractory LBCL setting [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 their cytotoxicity, expansion, intra-tumoral trafficking, and longevity in both *in vitro* and *in vivo* settings [14-17]. This benefit is 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 at 13% and 23% for axi-cel and tisa-cel, respectively, in the relapsed/refractory LBCL setting [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 grade 3/4 CRS rate of 3.6% across the total cohort. Our sensitivity analysis demonstrates that this low grade 3/4 CRS rate remains 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 second line setting [1] and 28% in 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 has 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 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 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 1 study to evaluate the safety and efficacy of BRT in patients with LBCL undergoing CART19 therapy (NCT05574114).

At present, we see several situations where BRT can benefit patients planned for CART19. Perhaps most importantly are when patients have lesion(s) which are symptomatic, where BRT can offer rapid palliation. There is now ample data to support that patients who have significant burden of metabolically active disease are likely to have poorer post-CART19 outcomes and greater toxicity, and BRT has demonstrated power to rapidly cytoreduce patients. Importantly, patients who are successfully cytoreduced appear to have similar outcomes to those with baseline low 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 perceived likelihood of local relapse after CART19; while these features warrant further study characteristics like 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 highly exciting but have 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 (**Supplementary Fig. 1**).

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 historical controls, even in patients with bulky disease. Ultimately, these results highlight the importance of disease control at time of CART19 infusion for subsequent toxicity and response and invite future prospective clinical trials incorporating BRT into innovative next-generation bridging concepts.

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Table 1.

Study's author/ No. of patients (total: 538)	CART19 product (%)	Age, Y, median (range)/ Gender (%)/ ECOG (%)	Histology (%)/ Stage (%)/ International prognostic index (IPI, %)	Bulky disease >7.5cm (%)	Line of therapy prior to CART19, median (range)/ Prior autologous stem cell transplant (%)	Systemic therapy during bridging (%)	Total radiation dose, Gy, median, (range)/ Fraction per course, median, (range)	Radiation regimen (focal vs. comprehensive)*	Response to BRT
Hubbeling et al/ **32**	Axicel 46% Tisacel 25% Lisocel 22% Brexucel 7%	66 (22-85) Male 73% Female 27% N/A	DLBCL: 78% MCL: 19% Burkitt: 3% I/II: 27% III/IV: 73% N/A	46%	3 (2-8) 20%	41%	30 Gy (4-54) 10 (2-30)	Comprehensive: 39% Focal: 61%	In-field ORR: 84%, Progression outside BRT field: 56%
Ladbury et al/ **12**	Axicel 100%	65 (21-75) Male 41.7% Female 58.3% PS2-3 25%	DLBCL: 91.7% tFL: 8.3% III/IV: 58.3% IPI ≥ 3: 16.7%	16.7%	2 (2-5) N/A	0%	20 Gy (4–40) N/A	Comprehensive: 66.7% Focal: 33.3%	N/A
Lutfi et al/ **14**	Axicel 100%	55.5 Male 28.6% Female 71.4%	DLBCL: 78.6% PMBCL: 7.1% tFL: 14.3% I/II: 64.3%	28.6%	2 (1-5) N/A	0%	N/A	N/A	N/A

		PS0: 35.7% PS1: 64.3%	III/IV: 35.7% IPI 0-1: 35.7% IPI 2: 42.9% IPI 3-5: 21.4%						
Pinnix et al/ 11	Axicel 100%	68 (51-84) Male 82% Female 18% PS2-3: 9%	DLBCL: 100% I/II:18% III/IV: 82% IPI ≥ 3: 55%	Defined as >10 cm: 36%	2 (2-3) N/A	0%	35.2 Gy (10-45)	Comprehensive: 64% Focal: 36%	N/A
Roddie et al/ 54	Axicel, Tisacel[#]	57 (49-65) Male 61.1% Female 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%	N/A	N/A	N/A
Saifi et al A/ 34	Axicel, Tisacel, Brexucel, Lisocel[#]	59 (19-73) Male 57.1% Female 42.9% N/A	DLBCL: 62.9% FL: 5.7% High-grade B-cell lymphoma 11.4% MCL: 2.9% N/A	Median bulk diameter 8.7 cm	N/A	15%	23.3 Gy (4-48)	N/A	N/A
Saifi et al B/ 14	Axicel, Tisacel, Brexucel[#]	50 (24-72) Male 42.9%	DLBCL: 85.7% tDLBCL: 7.1% High grade B-cell lymphoma:	N/A	2 (1-5) N/A	7.1%	20 Gy (15-36) 5 (3-24)	N/A	N/A

		Female 57.1% N/A	7.1% N/A						
Sim et al/ **11**	Axicel 100%	N/A	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) N/A	64%	20 Gy (6-30) 5 (3-10)	N/A	N/A
Wright et al/ **5**	Tisacel 60% Axicel 40%	N/A	DLBCL 84% tFL 13% PMBCL 3% II: 19% III: 16% IV: 65% N/A	Defined as > 10 cm: 40%	N/A	40%	37.5 Gy (20-45) 15 (5-20)	Comprehensive: 60% Focal: 40%	N/A
Fan et al/ **20**	Tisacel 90% 10%[#]	54.5 (35.8, 61.2) Male 65% Female 35% N/A	DLBCL 100% I: 10% II: 15% III: 10% IV: 65% IPI 0: 5% IPI 1: 15% IPI 2: 30% IPI 3: 35%	16.7%	35% received ≥4 N/A	25%	36 Gy (8-50)	N/A	N/A

			IPI 4: 15%						
van Meerten et al/ 14	Axicel 100%	N/A	N/A	N/A	N/A	0%	N/A	N/A	N/A
Jain et al/ 19	Axicel 100%	N/A	DLBCL 100%	N/A	N/A	0%	30 Gy (20-30.6) 10 (5-10)	Focal: 31.5% Unknown: 69.5%	N/A
Manzar et al/ 51	Axicel 78.4% Tisacel 3.9% Lisocel 17.7%	65 (24-87) Male 70.6% Female 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)	Comprehensive: 61% Focal: 40%	N/A
Saifi et al C/ 48	Axicel 81.3% Brexucel 8.3% Tisacel 6.2% Lisocel 4.2%	60 (19-84) Male 54.2% Female 45.8% N/A	DLBCL 62.5% FL 6.3% High-grade B-cell lymphoma 18.8% MCL 8.3% PMBCL 4.2% N/A	Median tumor size 6.8 cm, range (1.7-21)	2 (1-4) N/A	10.4%	25.5 Gy (9.3-43)	Comprehensive: 77% Focal: 23%	N/A
Ababneh et al/ 28	Axicel 64.3% Tisacel 35.7%	68.5 (21-82) Male 71.4%	DLBCL 50% FL 35.7% High-grade B-cell lymphoma 7.1%	Defined as ≥5 cm: 58.3%	N/A 17.9%	0%	N/A	N/A	N/A

		Female 28.6% PS0-1: 71.4% PS2-4: 28.6%	PMBCL 3.6% Unclassifiable B-cell lymphoma 3.6% I/II: 35.7% III/IV: 64.3% IPI ≥3: 64.3% IPI <3: 35.7%						
Kuhnl et al/ **129**	Axicel, Tisacel[#]	60 Male 62.8% Female 37.2% PS0: 55.2% PS1: 44.8%	DLBCL 69% tFL 21.7% PMBCL 4.7% Other 4.7% I/II: 38.7% III/IV: 61.3% IPI 0-2: 58.8% IPI ≥3: 41.2%	34.5%	27.9% received >2 17.8%	0%	30 Gy (2-39)	N/A	N/A
Bramanti et al/ **31**	Axicel 37.2% Tisacel 62.8%	57 (21–70) Male 67.7% Female 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% N/A	N/A	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)	Comprehensive: 48% Focal: 52%	N/A
Eigendorff et al/	Tisacel 100%	63 (50-73) Male 55%	DLBCL 100% N/A	Defined as ≥5 cm: 64%	55% received ≥3	0%	N/A	N/A	ORR: 45%

11		Female 45% N/A			27%				

Table 1. Patients and disease specific baseline characteristics. #subgroup percentage not provided. CART19: CD19-directed chimeric antigen receptor (CAR) T cells; ECOG: Eastern Cooperative Oncology Group; DLBCL: diffuse large B-cell lymphoma; tFL: transformed follicular lymphoma; PMBCL: primary mediastinal B-cell lymphoma; MCL: mantle cell lymphoma; axicel: axicabtagene ciloleucel; tisacel: tisagenlecleucel; lisocel: lisocabtagene maraleucel; brexucel: brexucabtagene autoleucel; N/A: not available. ORR: overall response rate.

*Radiotherapy is considered “comprehensive” if it treats all sites of PET avid (or regions suspicious for) lymphoma. Radiotherapy is considered focal if it is treating just some areas of PET avidity. Generally, focal irradiation is used for areas requiring palliation or for perceived higher risk lesions (i.e., bulky, extranodal, etc.).

Table 2.

Sensitivity Analysis / **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 wit potential patients overlap
Efficacy:					
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:					
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)
G 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)
Immune effector cell-associated neurotoxicity syndrome:					
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)
G 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)

Table 2. Sensitivity analyses results comparing reported main results using random-effect model to: 1. fixed-effect 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.

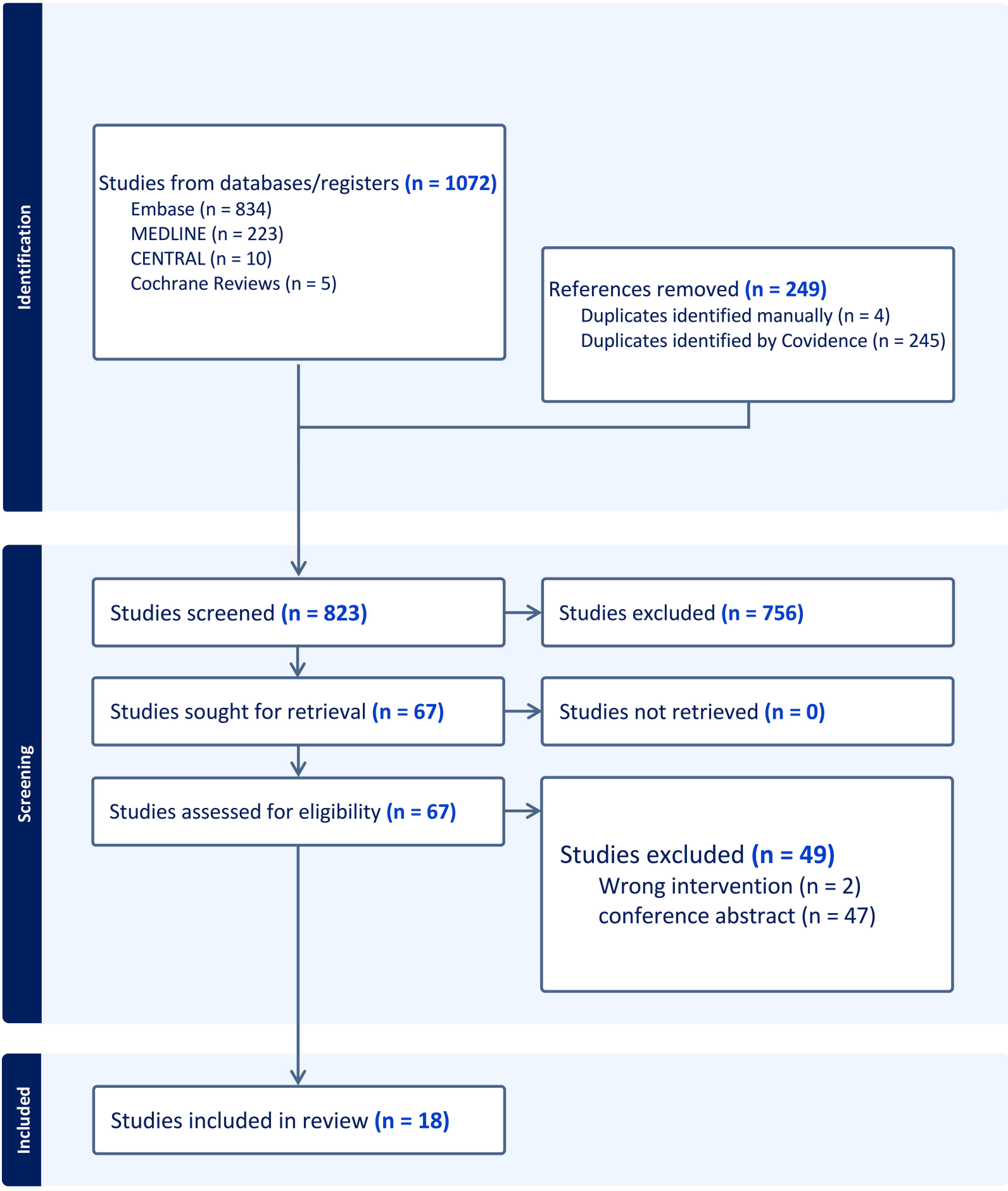
Figure legends:

Figure 1. Flowchart of the systematic review according to the PRISMA 2020 flow diagram.

Figure 2. Forest plots of overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) among patients from studies included in the meta-analysis. IV, inverse variance.

Figure 3. Forest plots of grade 3/4 cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) among patients from studies included in the meta-analysis. IV, inverse variance.

Figure 4. Meta-regression analysis comparing BRT studies to CMT studies outcomes represented as forest plots including grade 3/4 cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). IV, inverse variance. BRT, bridging radiation therapy. CMT, combined-modality treatment.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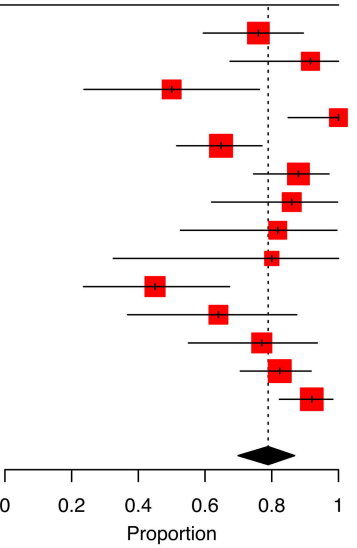
MEDLINE (n = 223)
CENTRAL (n = 10)
Cochrane Reviews (n = 5)
References removed (n = 249)
Duplicates identified manually (n = 4)
Duplicates identified by Covidence (n = 245)
Screening
Studies screened (n = 823)
Studies excluded (n = 756)
Studies sought for retrieval (n = 67)
Studies not retrieved (n = 0)
Studies assessed for eligibility (n = 67)
Studies excluded (n = 49)
Wrong intervention (n = 2)
conference abstract (n = 47)
Included
Studies included in review (n = 18)

ORR

Study	Events	Total	Weight	IV, Random, 95% CI
Hubbeling et al	24	32	8.5%	0.760 [0.595; 0.895]
Ladbury et al	11	12	5.9%	0.916 [0.675; 1.000]
Lutfi et al	7	14	6.4%	0.500 [0.237; 0.763]
Pinnix et al	11	11	5.7%	1.000 [0.849; 1.000]
Roddie et al	35	54	9.6%	0.648 [0.515; 0.771]
Saifi et al A	30	34	8.6%	0.880 [0.746; 0.972]
Saifi et al B	12	14	6.4%	0.860 [0.620; 0.997]
Sim et al	9	11	5.7%	0.818 [0.526; 0.995]
Wright et al	4	5	3.6%	0.800 [0.325; 1.000]
Fan et al	9	20	7.3%	0.450 [0.236; 0.674]
van Meerten et al	9	14	6.4%	0.640 [0.368; 0.875]
Jain et al	15	19	7.2%	0.770 [0.550; 0.936]
Manzar et al	42	51	9.5%	0.824 [0.706; 0.918]
Saifi et al C	44	48	9.3%	0.920 [0.823; 0.983]
Total (95% CI)	**339**	**100.0%**		**0.789 [0.699; 0.869]**

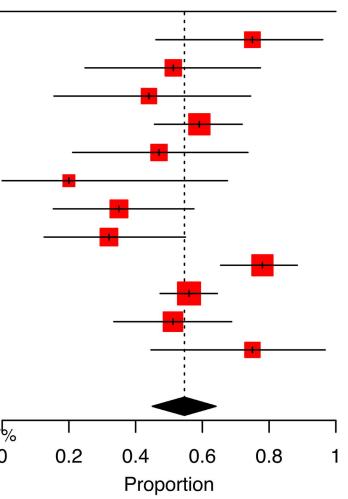
Heterogeneity: $Tau^2 = 0.0205$; $Chi^2 = 37.44$, df = 13 ($P < 0.01$); $I^2 = 65\%$



PFS

Study	Events	Total	Weight	IV, Random, 95% CI
Ladbury et al	9	12	6.4%	0.750 [0.461; 0.961]
Lutfi et al	7	14	7.0%	0.513 [0.248; 0.774]
Pinnix et al	5	11	6.1%	0.440 [0.155; 0.745]
Roddie et al	32	54	11.9%	0.591 [0.456; 0.719]
Saifi et al B	7	14	7.0%	0.470 [0.211; 0.736]
Wright et al	1	5	3.6%	0.200 [0.000; 0.675]
Fan et al	7	20	8.3%	0.350 [0.153; 0.575]
Jain et al	6	19	8.1%	0.320 [0.126; 0.549]
Manzar et al	40	51	11.7%	0.780 [0.655; 0.884]
Kuhnl et al	72	129	13.9%	0.560 [0.473; 0.645]
Bramanati et al	16	31	10.0%	0.512 [0.335; 0.688]
Eigendorf et al	8	11	6.1%	0.750 [0.446; 0.968]
Total (95% CI)	**371**	**100.0%**		**0.546 [0.450; 0.641]**

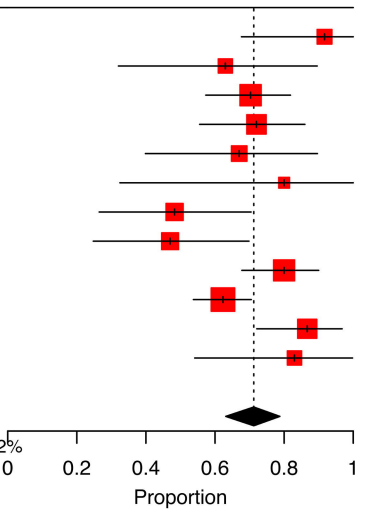
Heterogeneity: $Tau^2 = 0.0134$; $Chi^2 = 25.82$, df = 11 ($P < 0.01$); $I^2 = 57\%$



OS

Study	Events	Total	Weight	IV, Random, 95% CI
Ladbury et al	11	12	5.8%	0.917 [0.677; 1.000]
Pinnix et al	7	11	5.4%	0.630 [0.321; 0.896]
Roddie et al	38	54	12.0%	0.703 [0.573; 0.818]
Saifi et al A	24	34	10.1%	0.720 [0.556; 0.860]
Saifi et al B	9	14	6.4%	0.670 [0.399; 0.896]
Wright et al	4	5	3.1%	0.800 [0.325; 1.000]
Fan et al	10	20	7.8%	0.483 [0.265; 0.704]
Jain et al	9	19	7.6%	0.470 [0.248; 0.698]
Manzar et al	41	51	11.8%	0.800 [0.678; 0.900]
Kuhnl et al	80	129	14.8%	0.623 [0.537; 0.705]
Bramanati et al	27	31	9.7%	0.867 [0.721; 0.968]
Eigendorf et al	9	11	5.4%	0.830 [0.541; 0.998]
Total (95% CI)	**391**	**100.0%**		**0.712 [0.631; 0.788]**

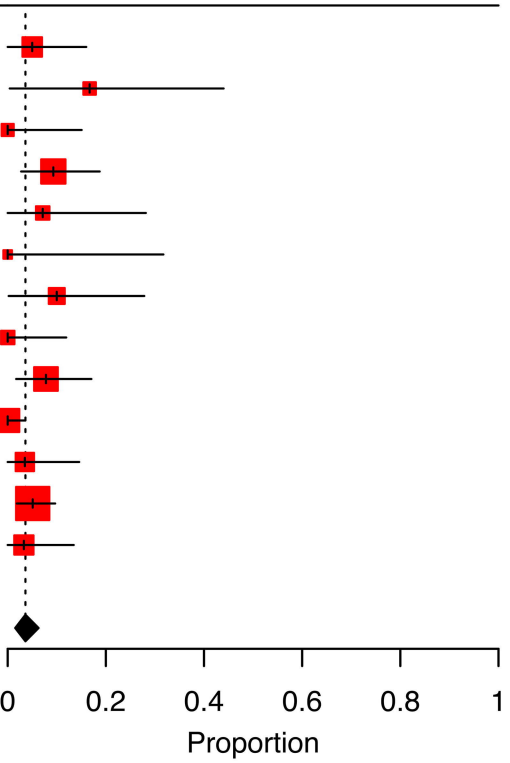
Heterogeneity: $Tau^2 = 0.0096$; $Chi^2 = 22.70$, df = 11 ($P = 0.02$); $I^2 = 52\%$



CRS (G3/4)

Study	Events	Total	Weight	IV, Random, 95% CI
Hubbeling et al	2	32	7.8%	0.050 [0.000; 0.160]
Ladbury et al	2	12	3.2%	0.167 [0.004; 0.440]
Pinnix et al	0	11	3.0%	0.000 [0.000; 0.151]
Roddie et al	5	54	12.1%	0.093 [0.027; 0.187]
Saifi et al B	1	14	3.7%	0.071 [0.000; 0.282]
Wright et al	0	5	1.5%	0.000 [0.000; 0.317]
Fan et al	2	20	5.2%	0.100 [0.002; 0.278]
van Meerten et al	0	14	3.7%	0.000 [0.000; 0.119]
Manzar et al	4	51	11.5%	0.078 [0.017; 0.171]
Saifi et al C	0	48	11.0%	0.000 [0.000; 0.036]
Ababneh et al	1	28	6.9%	0.035 [0.000; 0.146]
Kuhnl et al	7	129	22.7%	0.051 [0.019; 0.097]
Bramanati et al	1	31	7.6%	0.033 [0.000; 0.135]
Total (95% CI)		**449**	**100.0%**	**0.036 [0.015; 0.063]**

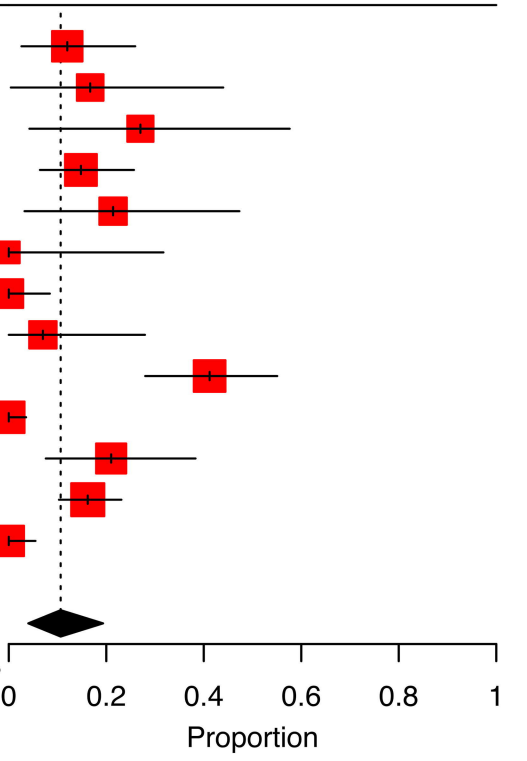
Heterogeneity: $Tau^2 = 0.0011$; $Chi^2 = 12.49$, df = 12 (P = 0.41); $I^2 = 4\%$



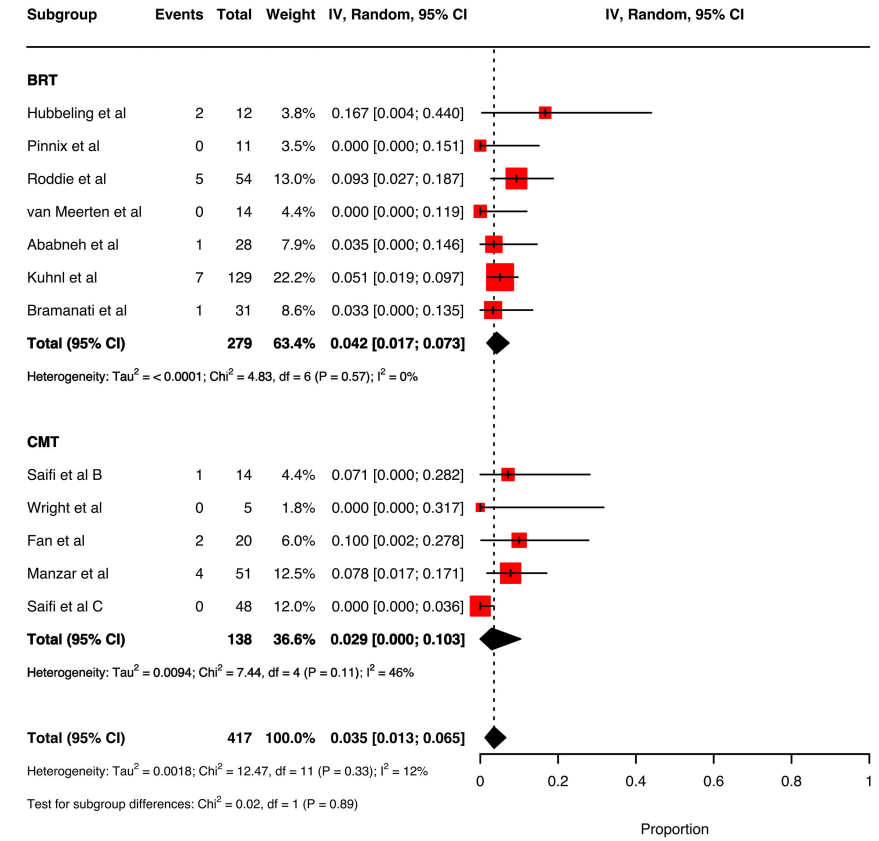
ICANS (G3/4)

Study	Events	Total	Weight	IV, Random, 95% CI
Hubbeling et al	4	32	8.4%	0.120 [0.026; 0.259]
Ladbury et al	2	12	6.4%	0.167 [0.004; 0.440]
Pinnix et al	3	11	6.2%	0.270 [0.042; 0.576]
Roddie et al	8	54	9.2%	0.148 [0.064; 0.257]
Saifi et al B	3	14	6.8%	0.214 [0.032; 0.473]
Wright et al	0	5	4.3%	0.000 [0.000; 0.317]
Fan et al	0	20	7.5%	0.000 [0.000; 0.084]
van Meerten et al	1	14	6.8%	0.070 [0.000; 0.279]
Manzar et al	21	51	9.1%	0.412 [0.280; 0.551]
Saifi et al C	0	48	9.0%	0.000 [0.000; 0.036]
Ababneh et al	6	28	8.2%	0.210 [0.076; 0.383]
Kuhnl et al	21	129	9.9%	0.162 [0.103; 0.231]
Bramanati et al	0	31	8.4%	0.000 [0.000; 0.055]
Total (95% CI)		**449**	**100.0%**	**0.106 [0.040; 0.193]**

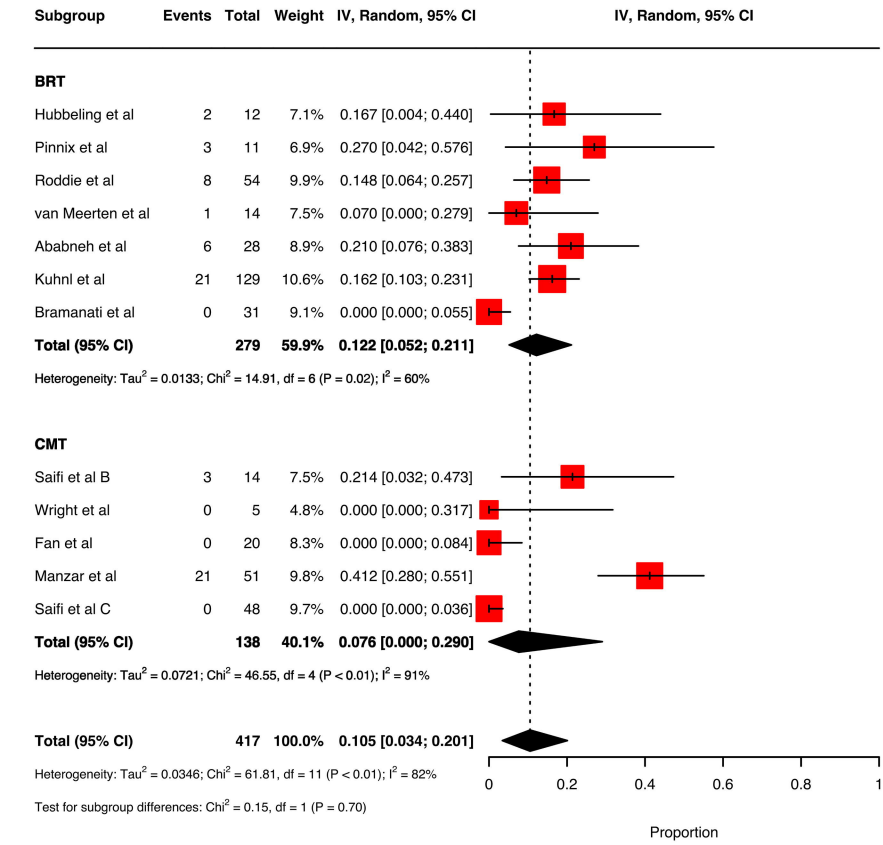
Heterogeneity: $Tau^2 = 0.0309$; $Chi^2 = 61.82$, df = 12 (P < 0.01); $I^2 = 81\%$



CRS (G3/4)

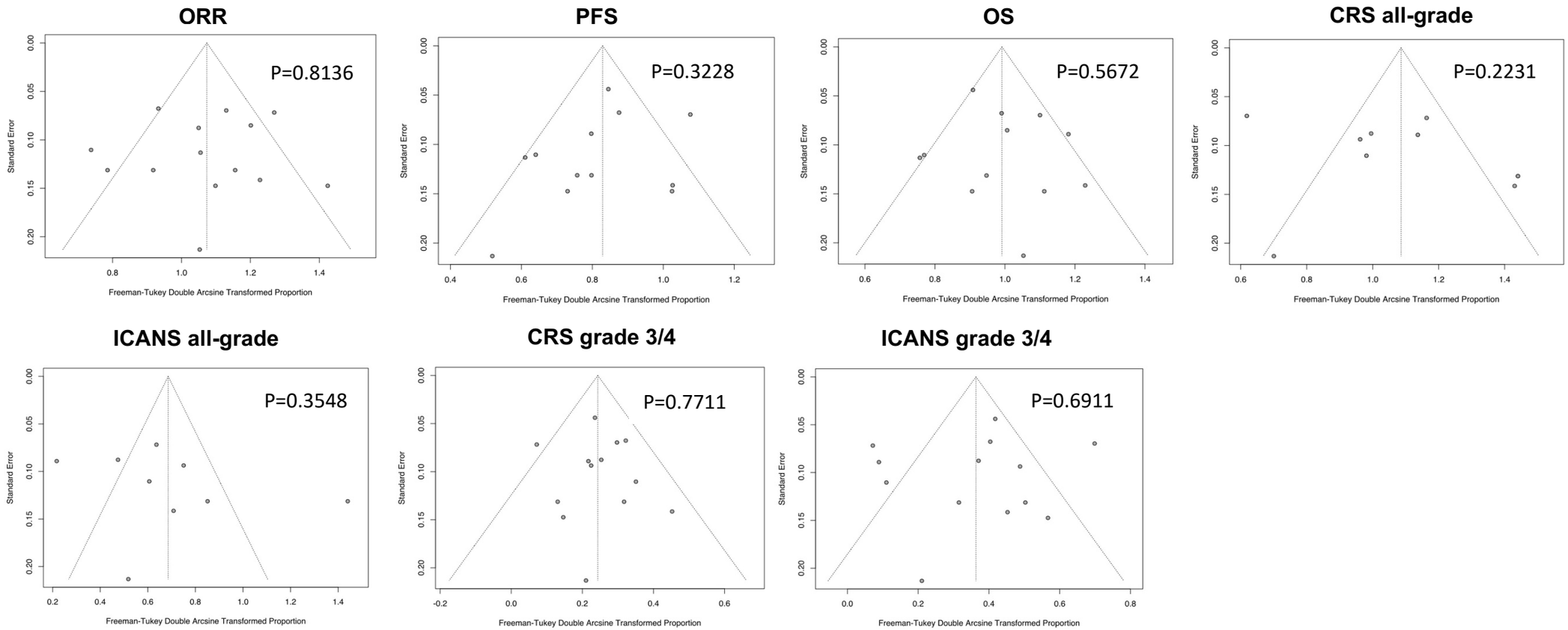


ICANS (G3/4)



Supplementary Materials

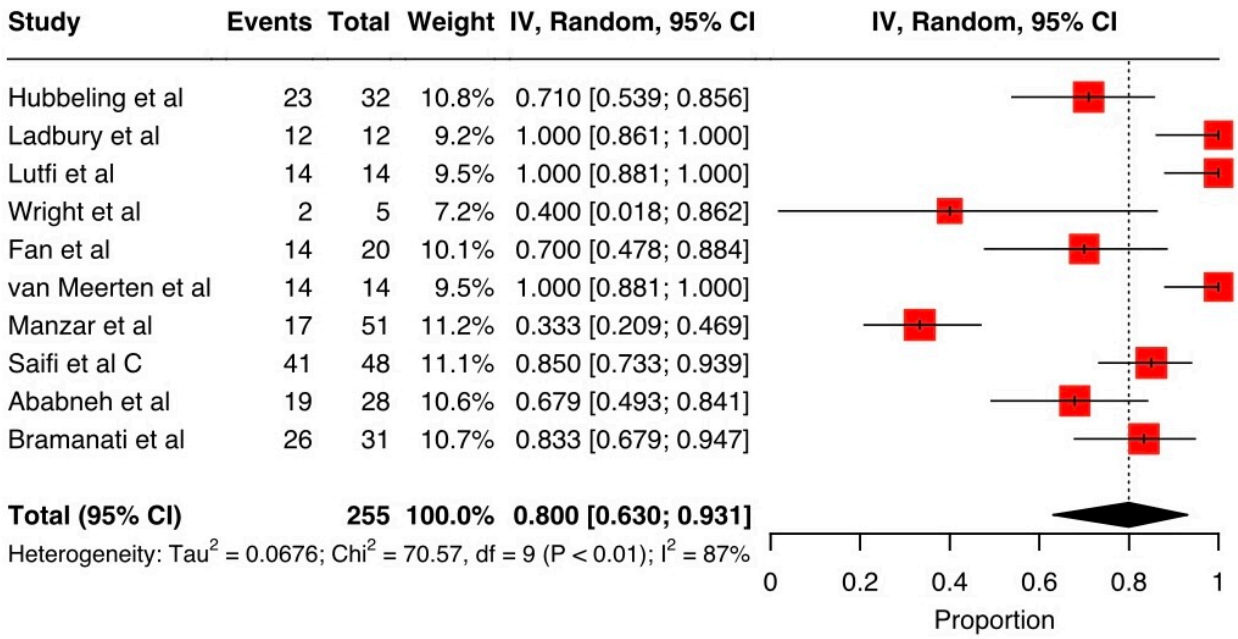
Supplementary Figure 1



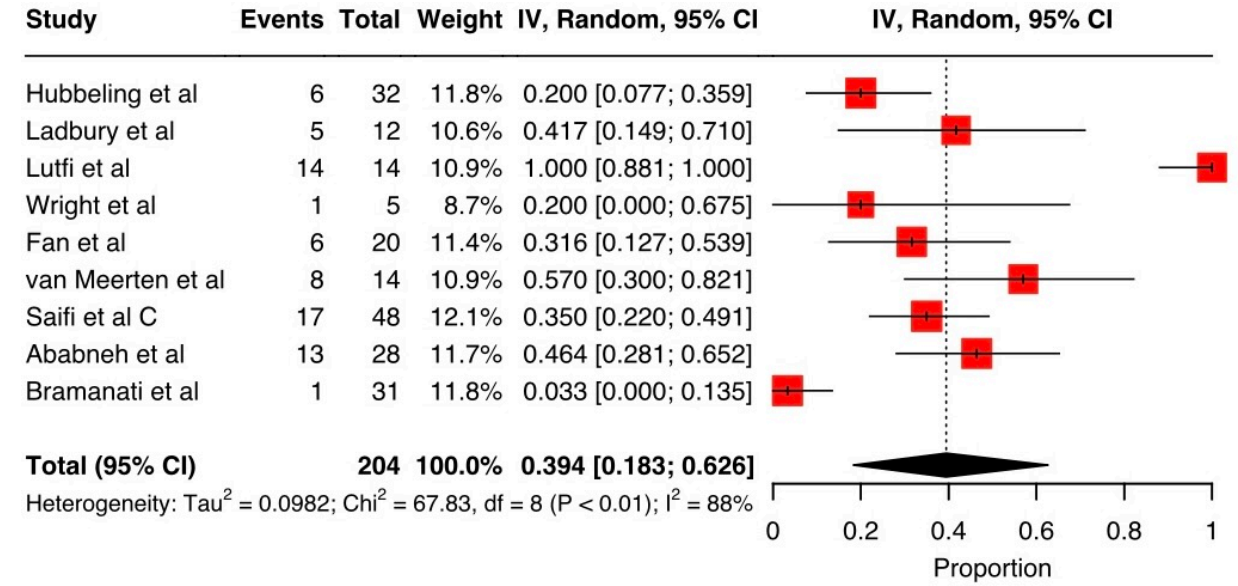
Supplementary Figure 1: Publication bias was analyzed by funnel plots. P-values for funnel plot asymmetry were derived from Egger tests.

Supplementary Figure 2

CRS all-grade

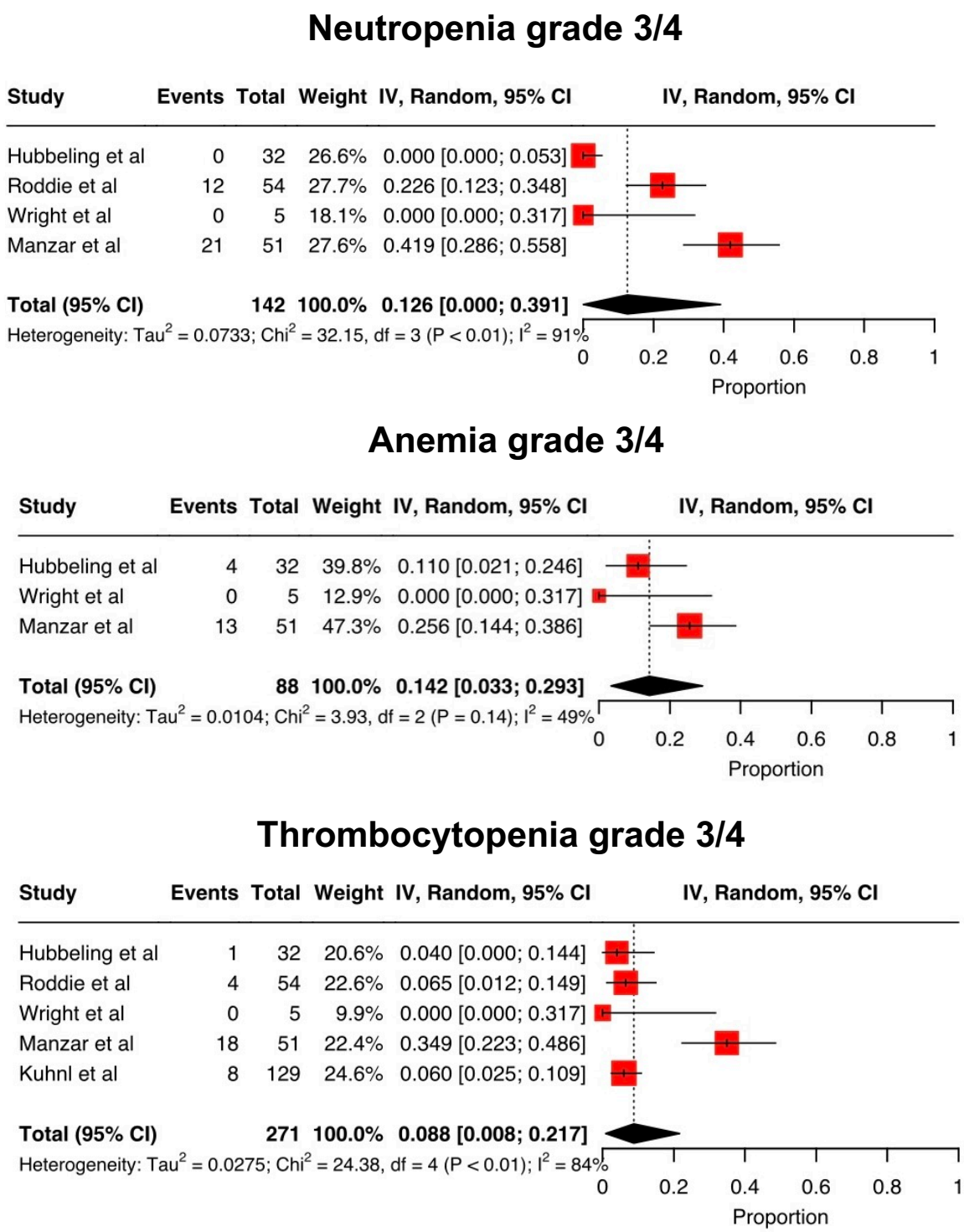


ICANS all-grade



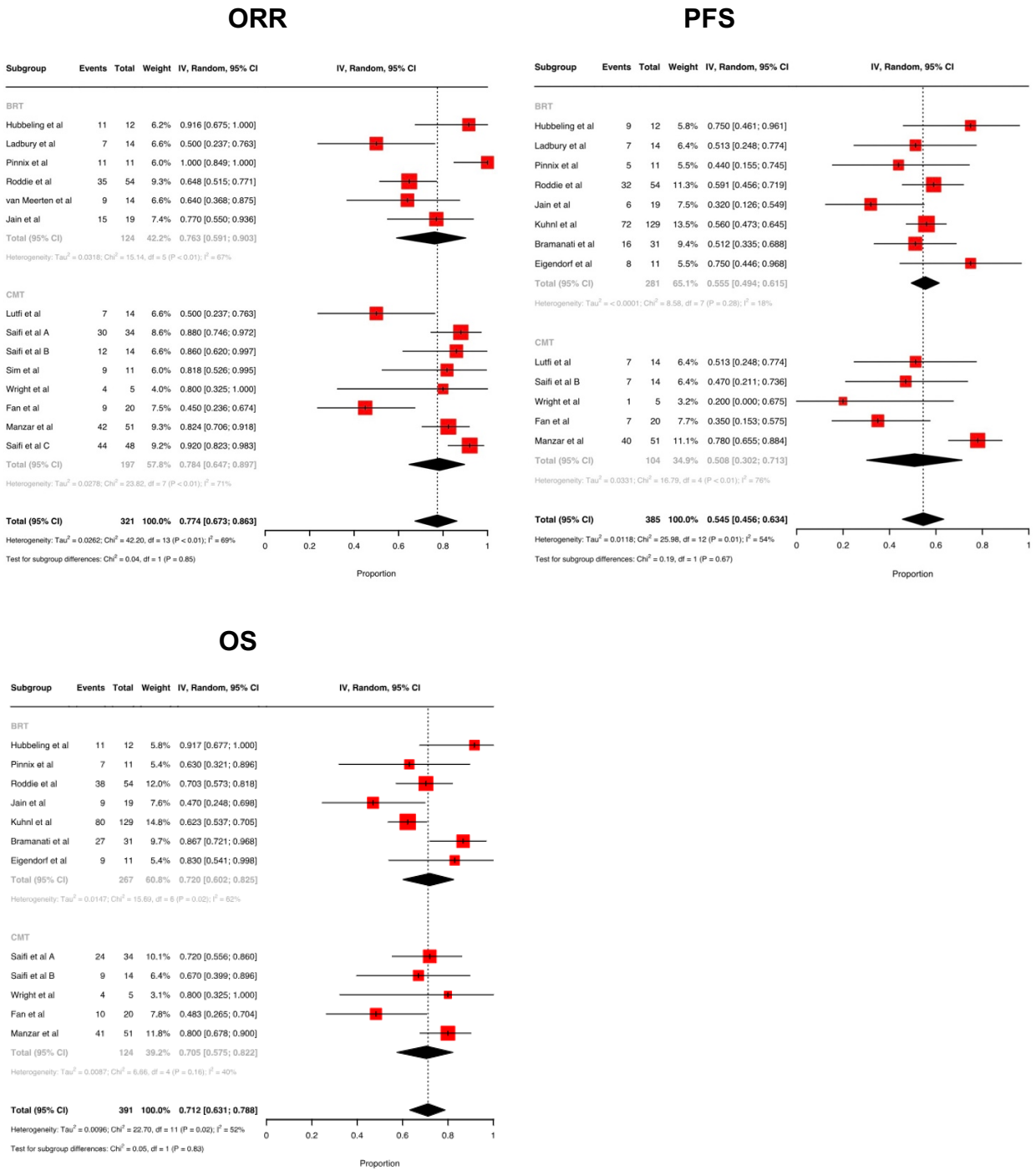
Supplementary Figure 2:
Forest plots of all-grade cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) among patients included in the meta-analysis. IV, inverse variance.

Supplementary Figure 3



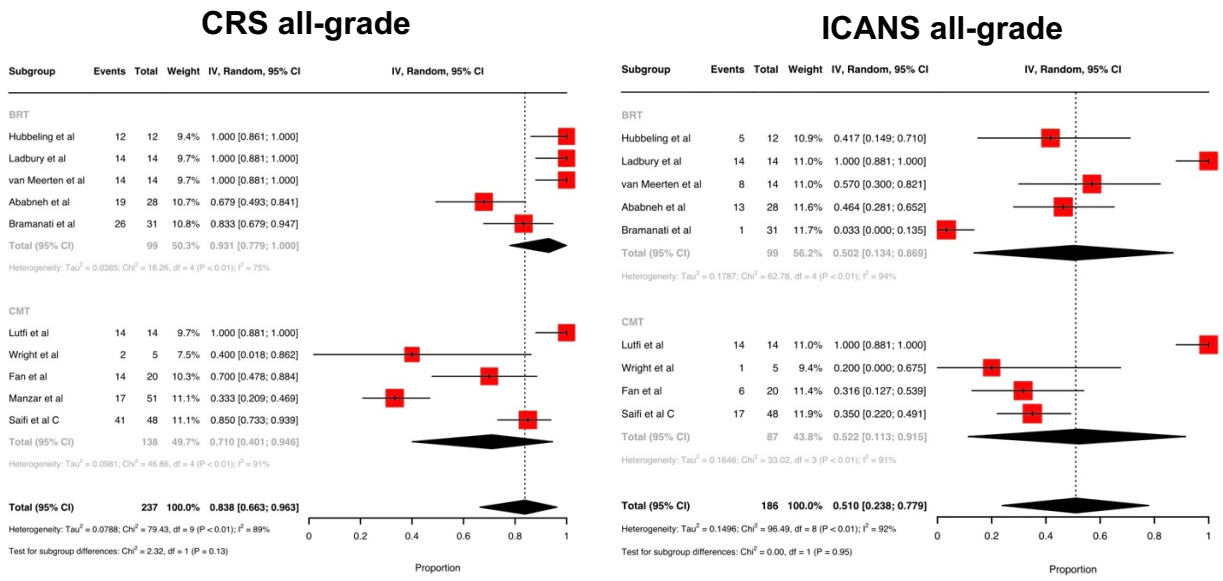
Supplementary Figure 3: Forest plots of grade 3/4 cytopenia among patients included in the meta-analysis. IV, inverse variance.

Supplementary Fig. 4



Supplementary Fig. 4. Meta-regression analysis comparing BRT studies to CMT studies outcomes represented as forest plots including overall response rate (ORR), progression-free survival (PFS), overall survival (OS). IV, inverse variance. BRT, bridging radiation therapy. CMT, combined-modality treatment.

Supplementary Fig. 5



Supplementary Fig. 5. Meta-regression analysis comparing BRT studies to CMT studies outcomes represented as forest plots including all-grade cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). IV, inverse variance. BRT, bridging radiation therapy. CMT, combined-modality treatment.

Supplementary Table 1

Line	**Ovid MEDLINE** (1946 to October 16, 2024): No language, publication date, or article type filters.
1	Immunotherapy, Adoptive/
2	(adoptive immunotherap* or adoptive cellular immunotherap* or chimeric antigen receptor or CAR T or CAR Tcell or "(CAR) T" or "(CAR) Tcell" or CAR engineered T cell or CAR engineered T lymphocyte or CAR modified T cell or CAR modified T lymphocyte).tw.
3	Receptors, Chimeric Antigen/
4	(chimeric t cell receptor* or artificial t-cell receptor* or chimeric immunoreceptor*).tw.
5	(axicabtagene ciloleucel or yescarta or axi cel or "fkc 876" or "fkc876" or "kte c19" or "ktec19" or lisocabtagene maraleucel or breyanzi or "jcar 017" or "jcar 17" or "jcar017" or "jcar17" or liso-cel or tisagenlecleucel or Kymriah or "cart 19" or "cart19" or "ctl 019" or "ctl019" or "lg 740" or "lg740").tw.
6	or/1-5
7	exp Lymphoma, Non-Hodgkin/
8	lymphoma*.tw.
9	(Non Hodgkin or "Non Hodgkin's" or Non Hodgkins or NHL or DLBCL or LBCL).tw.
10	(Burkitt leukemia or Burkitt's leukemia or Burkitts leukemia or Burkitt cell leukemia or Burkitt-type leukemia or Burkitt tumor or Burkitts tumor or Burkitt's tumor).tw.
11	or/7-10
12	exp Radiotherapy/ or Radiation Oncology/ or Radiotherapy Dosage/
13	(radiation* or radiotherap* or irradiation* or chemoradiotherap* or radiochemotherap* or radioimmunotherap* or xray therap* or x-ray therap* or roentgenotherap* or roentgen therap*).tw.
14	12 or 13
15	6 and 11 and 14
Line	**Ovid Embase** (1974 to October 16, 2024): No language, publication date, or article type filters.
1	adoptive immunotherapy/
2	(adoptive immunotherap* or adoptive cellular immunotherap* or chimeric antigen receptor or CAR T or CAR Tcell or "(CAR) T" or "(CAR) Tcell" or CAR engineered T cell or CAR engineered T lymphocyte or CAR modified T cell or CAR modified T lymphocyte).tw.
3	chimeric antigen receptor/
4	(chimeric t cell receptor* or artificial t-cell receptor* or chimeric immunoreceptor*).tw.
5	(axicabtagene ciloleucel or yescarta or axi cel or "fkc 876" or "fkc876" or "kte c19" or "ktec19" or lisocabtagene maraleucel or breyanzi or "jcar 017" or "jcar 17" or "jcar017" or "jcar17" or liso-cel or tisagenlecleucel ot Kymriah or "cart 19" or "cart19" or "ctl 019" or "ctl019" or "lg 740" or "lg740").tw.

6	or/1-5
7	nonhodgkin lymphoma/
8	lymphoma*.tw.
9	(Non Hodgkin or "Non Hodgkin's" or Non Hodgkins or NHL or DLBCL or LBCL).tw.
10	(Burkitt leukemia or Burkitt's leukemia or Burkitts leukemia or Burkitt cell leukemia or Burkitt-type leukemia or Burkitt tumor or Burkitts tumor or Burkitt's tumor).tw.
11	or/7-10
12	radiotherapy/ or radioimmunotherapy/ or radiation oncology/ or cancer radiotherapy/
13	(radiation* or radiotherap* or irradiation* or chemoradiotherap* or radiochemotherap* or radioimmunotherap* or xray therap* or x-ray therap* or roentgenotherap* or roentgen therap*).tw.
14	12 or 13
15	6 and 11 and 14
Line	**Cochrane Library (Wiley):** October 16, 2024. No language, publication date, or article type filters
#1	(adoptive immunotherap* or adoptive cellular immunotherap* or chimeric antigen receptor or CAR T or CAR Tcell or "(CAR) T" or "(CAR) Tcell" or CAR engineered T cell or CAR engineered T lymphocyte or CAR modified T cell or CAR modified T lymphocyte):ti,ab
#2	(chimeric t cell receptor* or artificial t-cell receptor* or chimeric immunoreceptor*):ti,ab
#3	(axicabtagene ciloleucel or yescarta or axi cel or "fkc 876" or "fkc876" or "kte c19" or "ktec19" or lisocabtagene maraleucel or breyanzi or "jcar 017" or "jcar 17" or "jcar017" or "jcar17" or liso-cel or tisagenlecleucel or Kymriah or "cart 19" or "cart19" or "ctl 019" or "ctl019" or "lg 740" or "lg740"):ti,ab
#4	#1 OR #2 OR #3
#5	(lymphoma* or Non Hodgkin or "Non Hodgkin's" or Non Hodgkins or NHL or DLBCL or LBCL):ti,ab
#6	(Burkitt leukemia or Burkitt's leukemia or Burkitts leukemia or Burkitt cell leukemia or Burkitt-type leukemia or Burkitt tumor or Burkitts tumor or Burkitt's tumor):ti,ab
#7	#5 OR #6
#8	(radiation* or radiotherap* or irradiation* or chemoradiotherap* or radiochemotherap* or radioimmunotherap* or xray therap* or x-ray therap* or roentgenotherap* or roentgen therap*):ti,ab
#9	#4 AND #7 AND #8

Supplementary Table 1: Systematic review search strategy.

Supplementary Table 2

Author	Year	Criterion 1: Inclusion criteria	Criterion 2: measurement of efficacy/safety	Criterion 3: identification of efficacy/ safety	Criterion 4: Consecutive Inclusion	Criterion 5: demographics	Criterion 6: Clinical information	Criterion 7: Follow-Up results	Criterion 8: Statistical analysis
Hubbeling et al.	2023	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Ladbury et al.	2023	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Lutfi et al.	2021	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Pinnix et al.	2020	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Roddie et al.	2023	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Saifi et al.	2023A	Yes	Yes/No	Yes/No	Yes	Yes	No	Yes	Yes
Saifi et al.	2022B	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Sim et al.	2019	Yes	Yes/No	Yes/No	Yes	Yes	No	Yes	Yes
Wright et al.	2020	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Fan et al.	2023	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Van Meerten et al.	2024	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Jain et al.	2024	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Manzar et al.	2024	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Saifi et al.	2024C	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Ababneh et al.	2024	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Kuhnl et al.	2024	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes

Bramanti et al.	2024	Yes	Yes/Yes	Yes/Yes	Yes	Yes	Yes	Yes	Yes
Eigendorff et al.	2024	Yes	Yes/No	Yes/No	Yes	Yes	No	Yes	Yes

Supplementary Table 2: Joanna-Brigg's Institute assessment of study bias. Criterion 5 (complete inclusion) was assessed within criterion 4. Criterion 9 (presenting sites'/clinics' demographics) was assessed within criterion 5.