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Publication Date

2021-10-01

DOI

10.1016/j.ejca.2021.07.036

European Journal of Cancer 156 (2021) 164–174

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Intention to treat versus modified intention-to-treat analysis in B-cell maturation antigen and CD19 chimeric antigen receptor trials: A systematic review and meta-analysis

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Received 6 April 2021; received in revised form 22 July 2021; accepted 27 July 2021
Available online 26 August 2021

KEYWORDS
Multiple myeloma;
BCMA;
CD19;
Leukaemia;
Chimeric antigen receptor therapy;
Intention to treat

Abstract ***Introduction:*** Chimeric antigen receptor T-cell therapy (CART) has revolutionised treatment of haematological malignancies; however, current reporting uses a modified intention-to-treat analysis (mITT) which over-estimates efficacy.

We assessed what proportion of CD19 and B-cell maturation antigen (BCMA) CART trials report the number of patients not receiving CART after being enrolled by performing meta-analysis of the mITT and intention-to-treat (iTT) overall response rate (ORR).

Methods: PubMed/MEDLINE, EMBASE and Cochrane databases were searched. All prospective clinical trials of CD19 and BCMA-targeting CART enrolling two or greater patients from 1st January 2013 to 1st November 2020 were included.

Results: A total of 28 BCMA CART and 74 CD19 CART trials were identified. These included 10 BCMA CART (35.7%) and 52 (70.2%) CD19 CART trials reporting total number of patients enrolled and number of patients treated with CART. For this cohort of trials, the mITT ORR for BCMA CART was 78.0% (95% confidence interval (CI) = 67.0–89.0%), and the iTT ORR was 70.0% (95% CI = 59.0–80.0%). For CD19 leukaemia CART, the mITT ORR was 87.2% (95% CI = 83.1–91.2), and the iTT ORR was 74.9 (95% CI = 64.8–85.0). For CD19 lymphoma CART, the mITT ORR was 70.7% (95% CI = 63.9–77.5), and the iTT ORR was 58.7% (95% CI = 49.7–67.7).

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https://doi.org/10.1016/j.ejca.2021.07.036

Conclusion: Across BCMA and CD19 CART trials, there is a difference of up to 8–12% in the ORR between modified and iTT analyses and a paucity of information regarding reasons why patients did not receive the intended study treatment.

1. Introduction

Chimeric antigen receptor T-cell therapy (CART) targeting CD19 has dramatically revolutionised the treatment landscape for relapsed/refractory acute lymphoblastic leukaemia and B-cell lymphomas, resulting in deep and durable remissions [1,2]. Use of CART targeting the B-cell maturation antigen (BCMA) in multiple myeloma (MM) also demonstrates impressive response rates, albeit with limited durability, in heavily pretreated patients and is now under consideration for formal approval by the US Food and Drug Administration [3].

There are, however, several logistic challenges associated with the administration of CART, including access to speciality centre care, delays with collection and production [3] and potential collection and manufacturing failures of the autologous CART product [4–6]. Subsequently, many patients may progress while awaiting therapy creating an inherent selection bias as patients whose disease progresses quickly are excluded from efficacy analyses. As a result, efficacy is reported in a modified intention-to-treat (mITT) manner for patients whose disease is clinically less aggressive.

In the present study, we aimed to assess what proportion of CD19 and BCMA-targeting CART trials reported the number of patients not receiving CART after being enrolled. For trials reporting this number, we performed a meta-analysis of both the intention-to-treat (iTT) and mITT of overall response rates (ORRs) and complete response rates (CRs) to estimate differences in efficacy. CD19 and BCMA CART were chosen as they represent the most commonly used CART in clinical practice/research [7].

2. Methods

This systematic review is reported as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations [8]. This review was retroactively registered on PROSPERO after the study was conceived, and data were collected/analysed (CRD42021237777).

2.1. Search strategy

Four databases were searched (Web of Science, MEDLINE/PubMed, EMBASE and Cochrane Registry of Controlled Trials). An example search strategy for BCMA CART is in Table S1. Two independent reviewers (GRM and TA) screened all studies, and any conflict was resolved through mutual discussion.

2.2. Inclusion and exclusion criteria

Our search strategy for both CD19 and BCMA CART trials was restricted to include all prospective trials exclusively enrolling at least two patients and published in an article or presented in an abstract form from 1st January 2013 through 1st November 2020. For CD19, all diagnoses (different subtypes of leukaemias and lymphomas) were included.

All other studies including editorials, case reports, case series and review articles were excluded. We aggregated data for all doses used in dose escalation strategies rather than just the recommended phase II dose. Whenever possible, we used the most recent data presented for these studies.

2.3. Data collection

Two authors (GRM and TA) performed and verified all data extraction. Extracted data were tabulated using Microsoft Excel (Microsoft, Redmond, Washington, United States). We identified the following characteristics of studies: type of product used; number of patients enrolled; whether the number of patients dropping out between enrolment and administration of CART was reported; number of previous lines of therapy received; minimal residual disease achievement; response rates; CRRs (relapsed/refractory); duration of response; and progression-free survival. We also collected data regarding reasons why patients were not included in efficacy analyses.

2.4. Outcomes

The primary outcome was the proportion of trials reporting the number of patients enrolled and those who actually received CART therapy.

Secondary outcomes were calculated for trials that reported on the number of patients who dropped out of the study after enrolment and before CART administration. Secondary outcomes included the ORR on an iTT analysis incorporating all enrolled patients.

The ORRs were defined as per the respective studies. This varied based on the disease being studied. For trials of MM, response criteria from the International Myeloma Working Group are commonly used that use a variety of assessments, including measurement of the

serum protein electrophoresis, a bone marrow biopsy assessment, and serum-free light chain measurement [9]. For lymphoma trials, response criteria commonly incorporate the Lugano criteria which primarily uses positron-emission tomography (PET)-computed tomography to assess for response and incorporates a 5-point grading scale based on the degree of PET avidity [10].

2.5. Calculating iTT analysis

We investigated individual trials to identify discrepancies between the total number of enrolled patients and the number of patients included in outcome analyses as reported by the authors of each study. We investigated the reasons for these differences.

Patients were considered nonresponders for the purposes of our analysis and included in the denominator of the iTT analysis for reasons such as 'lost to follow-up,' 'manufacture failure,' 'death,' 'progression before CART' and 'other/not listed.'

Patients were not included in the denominator of the iTT analysis for reasons such as 'received nonconforming product,' 'not yet evaluable for response,' 'insufficient follow-up to assess for efficacy' or 'achievement of PET negativity or response before CART.' We did not include these patients in the denominator of our iTT analysis as we could not assume that these patients were not responders (especially patients who had already obtained a complete response before CART administration).

2.6. Statistical methods

Outcomes were reported in proportions and pooled using the DerSimonian-Laird method. The DerSimonian-Laird method is the most commonly used random-effects model that summarises evidence about treatment efficacy from a number of related clinical trials [11]. OpenMetaAnalyst (Brown University) was used for analysis. The I2 statistic was used to test for heterogeneity between the studies. The I2 of values of <30%, 30–60%, 61–75% and >75% were suggestive of low, moderate, substantial and considerable heterogeneity, respectively [12].

Sensitivity analyses included Begg and Egger statistics and a Galbraith plot [13]. The influence of individual studies was examined by leaving out one study and recalculating the meta-analysis. We assessed publication bias by designing funnel plots [13].

3. Results

3.1. BCMA CART for multiple myeloma

A total of 28 BCMA CART clinical trials for MM met inclusion criteria (Fig. 1). Table 1 lists characteristics of these studies.

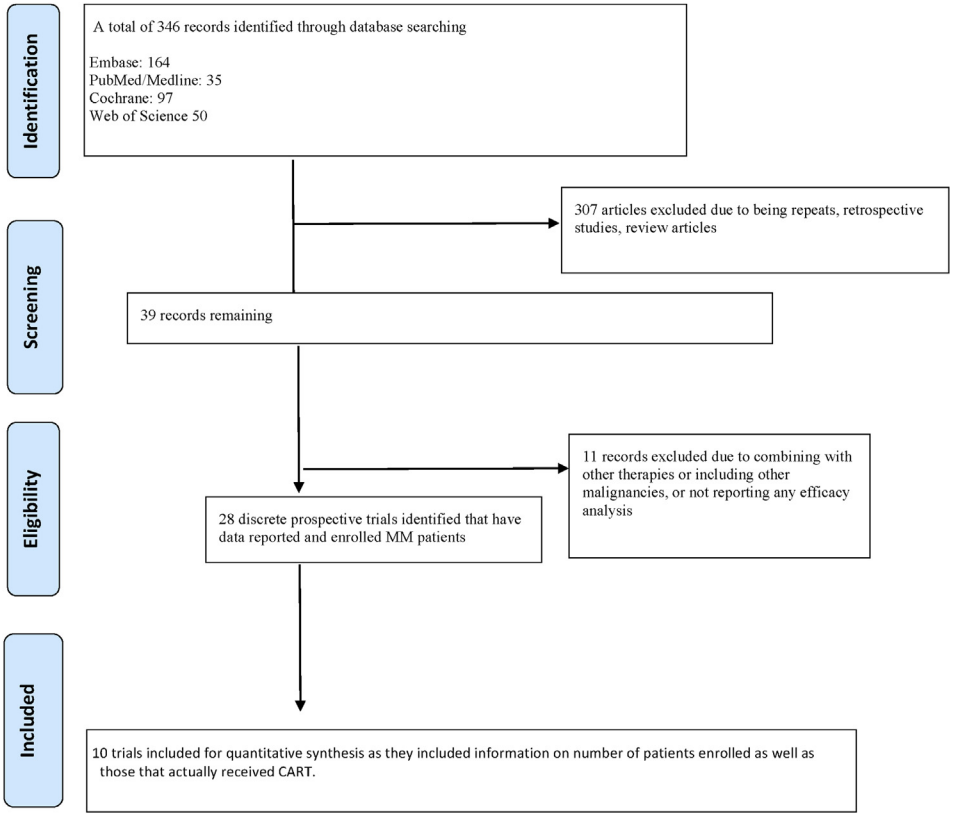

Fig. 1. Flow diagram representing study selection for BCMA CART studies. BCMA, B-cell maturation antigen; CART, chimeric antigen receptor T-cell therapy.

Table 1
Characteristics of multiple myeloma chimeric antigen receptor therapy trials.

Author	Reporting*	Product Name	Year reported	Number of patients (for efficacy)	Median Prior Lines of Therapy	ORR (%)	MRD (%)	mDOR (m)	mPFS (m)
Kochenderfer [23]	N	NR	2016	12	NR	25.0	NR	NR	NR
Liu [24]	N	NR	2018	18	NR	92.9	NR	NR	NR
Mailankody [25]	N	MCARH171		11	6	63.6	NR	3.5	NR
Brudno [26]	N	NR		24	9.5	58.3	50.0	NR	NR
Green [27]	N	NR		7	8	100.0	NR	NR	NR
Hu [28]	N	NR	2019	33	NR	96.9	97.9	NR	70.7% 1 year
Li [29]	N	BM38		16	NR	87.5	87.5	NR	NR
Yan [30]	Y	NR		21	6	95.2	80.9	NR	NR
Garfall [31]	Y	CTL119		10	3.6	90.0	50.0	NR	NR
Cohen [32]	Y	CAR-BCMA		25	7	48.0	20.0	4.1	NR
Wang [33]	N	LCAR-B38M		57	NR	87.7	68.4	22.0	20.0
Fu [34]	N	NR		44	NR	79.5	36.3	NR	15.0
Popat [35]	Y	AUTO2		7	5	42.9	NR	NR	NR
Cowan [36]	Y	NR		7	10	85.7	71.4	NR	NR
Mikkilineni [37]	Y	FHVH-BCMA-T		12	6	83.3	NR	NR	NR
Li [38]	N	CT103A	2020	18	NR	100.0	NR	NR	NR
Mailankody [39]	N	Orva-cel		62	6	91.9	NR	NR	NR
Lin [22]	Y	bb2121		62	NR	75.8	48.4	18.1	8.8
Alsina [40]	N	bb21217		59	6	67.8	NR	6.0	NR
San Miguel [41]	Y	Ide-cel		128	6	72.7	NR	10.6	8.6
Han [42]	N	NR		34	10	88.2	NR	NR	NR
Hao [43]	N	CT053		24	4.5	87.5	70.8	21.8	18.8
Costello [44]	N	P-BCMA-101		30	7	66.7	NR	NR	NR
Madduri [45]	Y	Cilta-cel		97	6	96.9	50.5	NR	NR
Kumar [46]	N	CT053		18	5	94.4	61.1	NR	NR
Jiang [47]	N	GC012F		16	5	93.8	68.8	NR	NR
An [48]	N	C-CAR088		21	4	95.2	NR	NR	NR

MRD, measurable residual disease; mDOR, median duration of response; mPF, median progression free survival; ORR, overall response rate.

Amongst these 28 clinical trials, 10 trials (35.7%) reported clearly on the number of patients enrolled and the number actually receiving CART.

3.2. ORR

The pooled ORR for these 10 studies on mITT was 78.0% (95% confidence interval (CI) = 67.0–89.0%, I2 = 87.90%) (Fig. 2).

We performed an iTT analysis for these studies by including all patients including those who were enrolled and did not subsequently receive CART or were not included in efficacy analysis for reasons mentioned in the methods. The pooled ORR on an iTT was 70.0% (95% CI = 59.0–80.0%, I2 = 80.6%) (Fig. 3).

3.3. Reasons for not including patients in efficacy analysis

Amongst the 10 BCMA trials reporting on the number of patients enrolled but not receiving CART, a total of 395 patients were enrolled and received CART with results of their efficacy reported. An additional 46 patients did not receive CART after enrolling. For six of these patients, the reason for not receiving CART was rapid disease progression necessitating alternative therapy; however, for the remainder of the 40 patients (86.9%), the reasons were not reported.

An additional 47 patients from the 28 BCMA trials were excluded from efficacy analysis despite receiving CART. For 46 of these patients, the reason was an insufficient follow-up to assess for efficacy (97.8%), whereas one patient (2.2%) was excluded owing to an early death from infection before efficacy could be analysed.

3.4. CD19 CART

A total of 74 CD19 CART studies were identified, with the characteristics of all studies included listed in Table S2.

Amongst these 74 clinical trials, 52 trials (70.2%) reported the total number of patients who were enrolled and those who received CART.

CD19 studies were substratified into those that exclusively studied leukaemia or lymphoma. For 26 studies that exclusively enrolled patients with leukaemia, the pooled ORR on mITT was 87.2 (95% CI = 83.1–91.2), with moderate heterogeneity (I2 = 56.6%). On an iTT analysis, the pooled ORR was 74.9 (95% CI = 64.8–85.0), with high heterogeneity (I2 = 92.3%) (Fig. 4ab).

For the 14 studies that exclusively enrolled patients with lymphoma, the pooled response rate on modified iTT

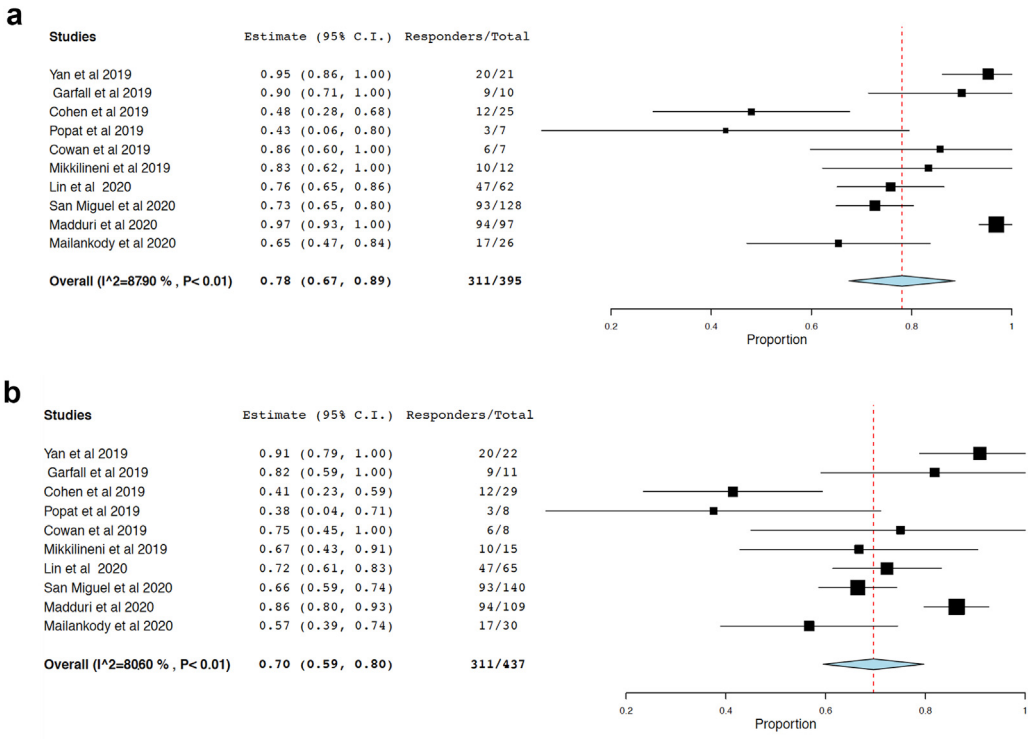

Fig. 2. a: The overall response rate by modified intention-to-treat analysis of BCMA CART for studies reporting the number of patients enrolled and those receiving therapy. b: The overall response rate by intention-to-treat analysis of chimeric antigen receptor therapy for BCMA studies that reported clearly on the number of patients enrolled and those who actually received CART. B-cell maturation antigen; CART, chimeric antigen receptor T-cell therapy.

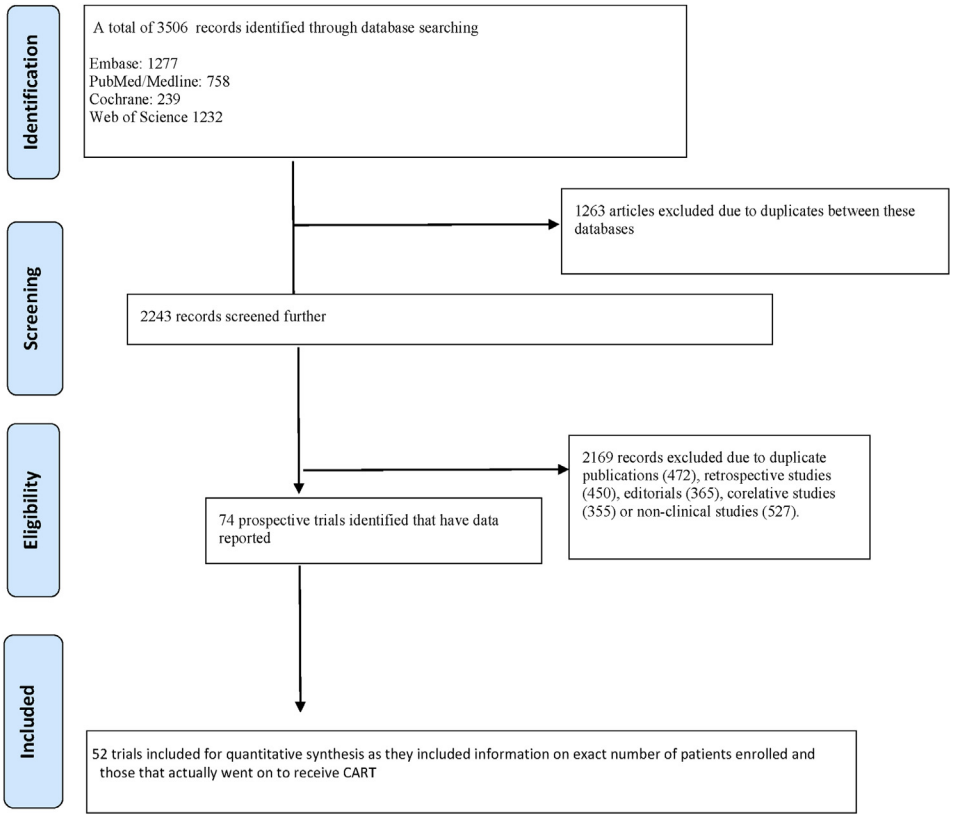

Fig. 3. Flow diagram representing study selection for CD19 CART studies. CART, chimeric antigen receptor T-cell therapy.

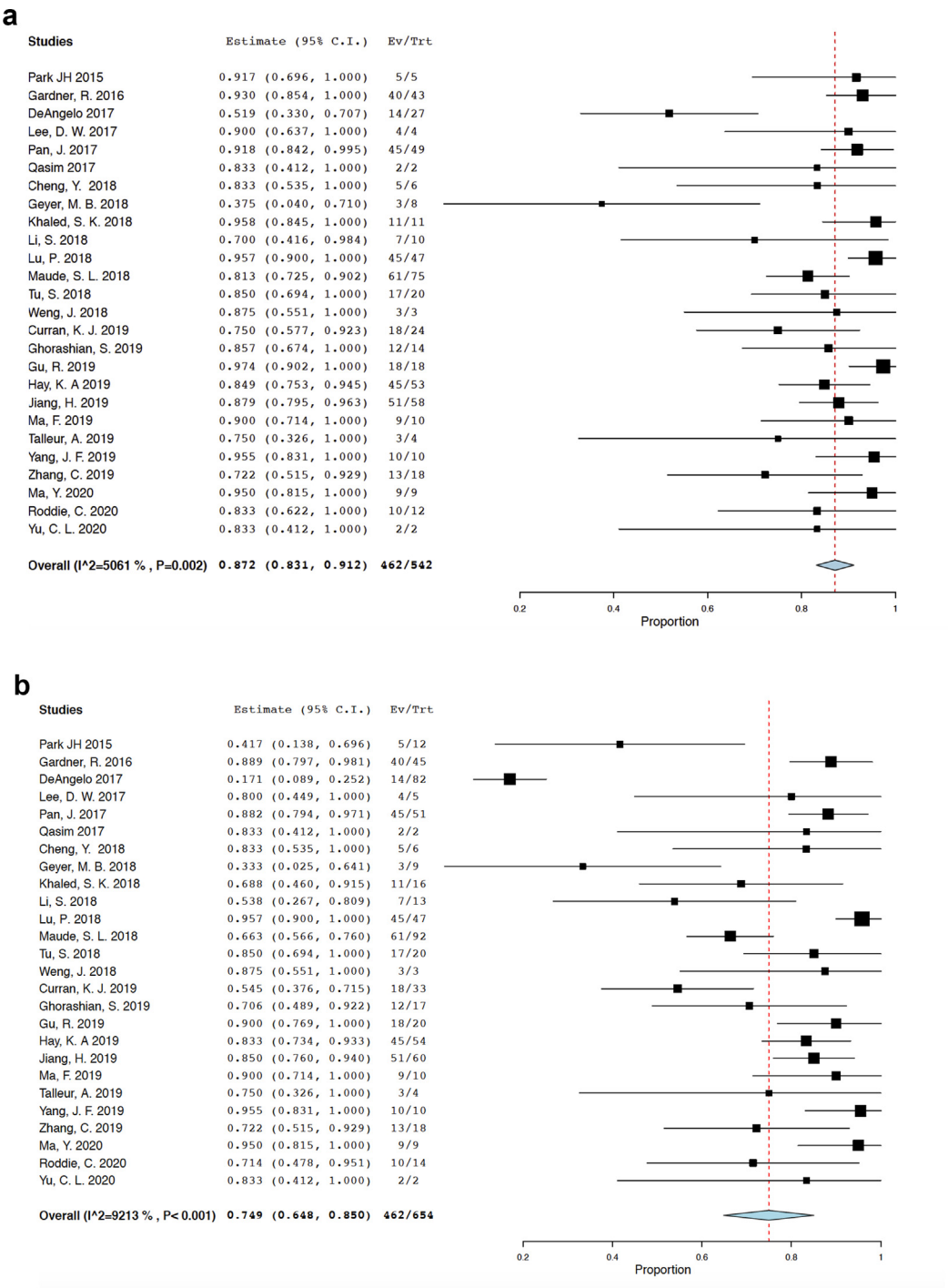

Fig. 4. a: The pooled overall response rate by modified intention-to-treat analysis of CD19 chimeric antigen receptor therapy for leukaemia studies that reported clearly on the number of patients enrolled and those who actually received CART. b: The overall response rate by intention-to-treat analysis of CD19 chimeric antigen receptor therapy for leukaemia studies that reported clearly on the number of patients enrolled and those who actually received CART. CART, chimeric antigen receptor therapy.

analysis was 70.7 (95% CI = 63.9–77.5), with moderate heterogeneity (I2 = 54.7%). On an iTT analysis, the pooled ORR was 58.7 (95% CI = 49.7–67.7), with high heterogeneity (95% CI = 92.13) (Fig. 5ab).

For all 52 CD19 studies including those that enrolled a variety of CD19 malignancies, the pooled ORR when calculated on mITT analysis was 79.0% (95% CI = 74.8–83.2%, I2 = 73.9%). The pooled ORR for

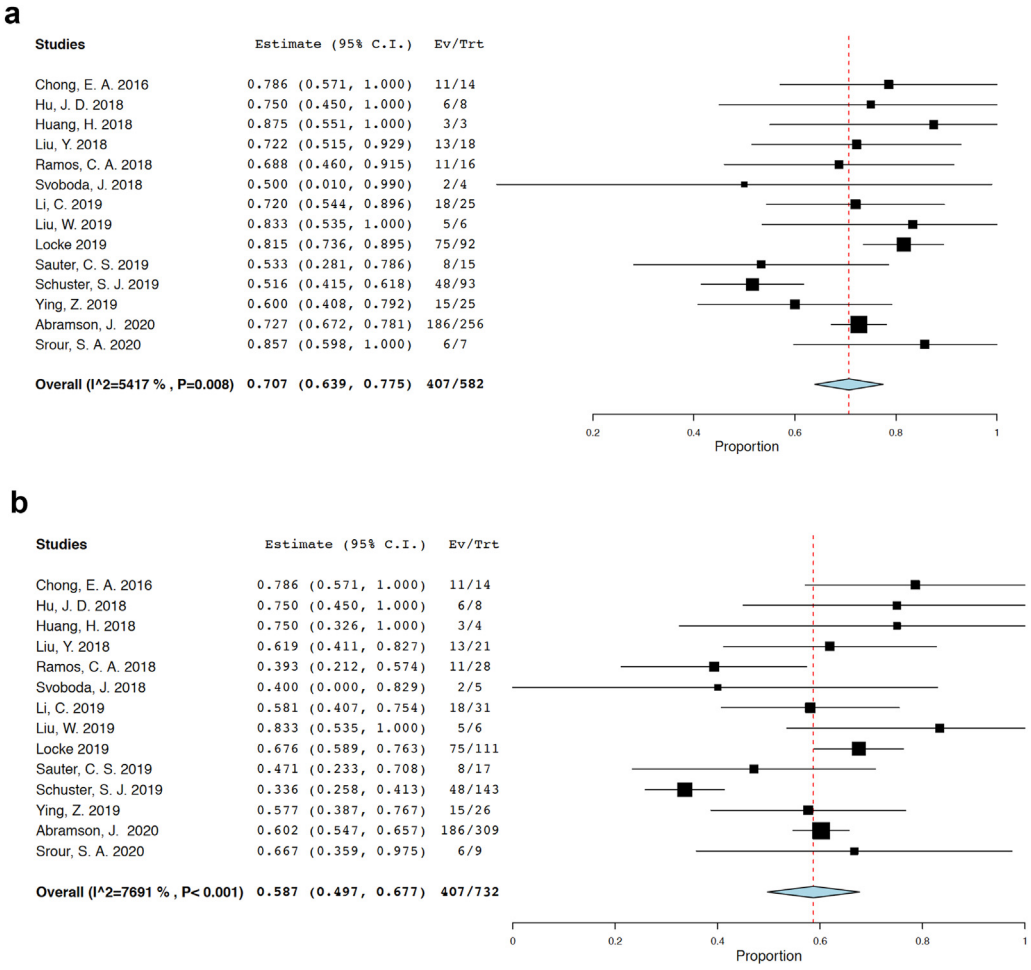

Fig. 5. a: The pooled overall response rate by modified intention-to-treat analysis of CD19 chimeric antigen receptor therapy for lymphoma studies that reported clearly on the number of patients enrolled and those who actually received CART. b: The overall response rate by intention-to-treat analysis of CD19 chimeric antigen receptor therapy for lymphoma studies that reported clearly on the number of patients enrolled and those who actually received CART. CART, chimeric antigen receptor T-cell therapy.

an iTT analysis was 68.1% (95% CI = 61.3–74.8, I2 = 90.3%) (Supplementary Fig. 1a and 1b).

3.5. Reasons for not including patients in efficacy analysis

Amongst the 52 CD19 trials that reported on the total number of patients enrolled, 28 trials enrolled patients who did not subsequently receive CART, whereas in the other 24 studies all enrolled patients went on to receive CART.

In these 28 studies, 266 patients did not receive CART after enrolling. The most common reasons for not receiving CART after enrolling were as follows: not reported or other reasons (121, 45%); death (49, 18%); difficulties with manufacturing CART (38, 14%); response to prior therapy/conditioning rendering them ineligible for CART (22, 8%); progression of disease or disease-related complications (21, 8%); infection (10, 4%); and patients not having received CART yet owing to insufficient follow-up at time of analysis (5.2%).

An additional 113 patients from these 52 trials were excluded from the efficacy analyses of these studies despite receiving CART. The reasons were as follows: not reported/other (35, 31%); not yet evaluable for response (29,26%); received nonconforming product (25, 22.1%); death (9.8%); inability to obtain PET scan before treatment (6, 5%); achievement of measurable residual disease (MRD) negativity/PET response before administration of product (5, 4%), CART given at a greater than maximum dose (2, 2%) and loss to follow-up (2, 2%).

3.6. Sensitivity analysis

The funnel plot, Galbraith plot and Begg and Egger statistics indicated a slight small study bias (Begg statistic p-value = 0.037) with most studies having similar precision (Supplementary Figs. 2–4).

Omitting single studies successively showed no study had a significant influence on the overall results (Supplementary Figs. 5 and 6) for both BCMA and CD19 leukaemia CART.

A metaregression was performed for studies with 10 or greater participants versus less than 10 participants for all CD19 studies. Results indicated no significant effect on the overall results by size of the study. A cumulative meta-analysis was also performed (Supplementary Fig. 6) showing that the CIs based on the cumulative meta-analysis agree with the overall conclusions starting at the earliest publication dates.

4. Discussion

CART has undoubtedly changed the paradigm of treatment for patients with haematological malignancies, with prolonged and durable remissions noted for a subset of patients, especially with CD19 therapies [1,2,7]. For commercially approved products such as axicabtagene ciloleucel, the efficacy has also been reproduced in real-world data sets on a mITT analysis of patients successfully receiving CART [14]. However, this study also reported analysis only for patients actually receiving CART. Unfortunately, our study demonstrates a lack of universal reporting of drop-out (owing to disease progression/production failure) after enrolment and before administration of therapy in BCMA and CD19 CART trials. Furthermore, the reasons for why patients do not receive CART after enrolling are not clearly reported.

When reported, there often is a decline in the number of patients from the time of enrolment to the time of actual administration of CART. This results in a noticeable drop-in response rate and may limit the external validity of these studies. Across both MM BCMA and leukaemia/lymphoma CD19 CART trials, the difference between response rates on iTT and mITT analyses was up to 8–12%.

Our results are concordant with a small cohort of real-world patients with diffuse large B-cell lymphoma (DLBCL) for which an iTT analysis of CART was performed showing only 73% of patients for whom CART was intended actually received the treatment [15].

These findings have implications on the true efficacy of CART for patients with haematologic malignancies. It is important to note that our study does not account for other limitations in access to CART and other sources of selection bias in these trials. Diagnosis to treatment interval is a well-known prognostic feature for DLBCL [16], and patients able to wait to start treatment inherently have less aggressive disease and better outcomes. The waitlists for enrolment on CART studies may filter out patients with aggressive disease biology who cannot wait for completion of cell manufacturing.

With the advent of off-the-shelf immunotherapies such as bispecific targeting agents that link immune effector cells to a target, the administration and production process of CART in its current state represents a significant hindrance to its routine use for a broader population of patients [17]. It is anticipated that use of allogenic CART products, as recently shown by Mailankody et al. for MM [18] or administration of CART as an outpatient by Costello et al. [19], may alleviate some of the practical limitations associated with CART.

We observed higher reporting rates for CD19 CART as opposed to BCMA CART, likely owing to the fact that there is a longer follow-up for CD19 CART as these products are now in later stages of clinical development.

Limitations are that the studies we included have small sample sizes with significant statistical heterogeneity between the studies. Use of the random effects model controls for this between-study variability that may not have been evident if studies were larger. In our analysis, we have pooled a number of haematological diseases, at different stages and in different contexts such as pre-emptive CART, in a tandem with transplantation and so on. This leads to a heterogeneous group of studies included in our analysis. The heterogeneity of our studies was higher in our iTT analysis than in mITT analysis. This could be attributable to a wide variation between studies of the number of patients who were removed from analysis of efficacy on the mITT analysis. As a result, the denominator for the iTT analysis varied considerably depending on how many patients were removed from the efficacy analysis. The duration of follow-up is short, and there is limited reporting on duration of response and progression-free survival for BCMA and CD19 CART. This precludes a quantitative synthesis for comparison for those outcomes. We used the response rate for estimates of efficacy as that was most commonly reported by the included studies. However, the response rate is a surrogate outcome, and this may not corelate with longer survival or improved outcomes for patients [20]. Because reasons for not including patients in efficacy analysis were not always listed, assumptions were made about responses. Although this is a limitation of our study, it highlights the importance of reporting why each patient is excluded from an efficacy analysis. A significant proportion of studies we analysed were abstracts and may go on to report the difference between the number of enrolled patients and those who actually received CART in the final article, as shown by the aforementioned difference in BCMA and CD19 reporting rates. There were instances where an earlier published article reported on patients who had progressed before receiving CART, but the most recent update did not have that information [21,22]. We also recognise that despite the efforts of two reviewers to screen all literature in this space, our search strategy may have missed some studies and most recent updates given the rapidly evolving landscape in this field.

Prospective collection of 'real-world' data is needed using large databases would help provide further insight into our findings. Such real-world data should include not only for patients who receive CART but also those who were screened and did not receive CART and those who undergo leukapheresis but were unable to receive CART subsequently. Transparent reporting of subsequent and ongoing clinical trials of efficacy outcomes in both an iTT and mITT analysis would be important to help further elucidate the results of our study and allow a realistic interpretation of the true efficacy and applicability of this therapy. Mandating reporting of iTT analysis by journals and societies may also aid in this endeavour.

CART is a revolutionary treatment modality, and responses are impressive even on iTT analyses; however, current reporting on mITT analyses may overestimate response rates, and real-world response rates may thus be lower than those reported in clinical trials. For this reason, transparent reporting of the number of patients unable to receive CART after enrolment and reasons for this are necessary to accurately estimate efficacy and better inform clinical practice.

Author contribution

GRM and VP conceived the research idea. GRM, TA and NA collected data and performed the literature review. GRM and MA performed initial statistical calculations. IA performed supplementary analysis and supervised all statistical calculations. GRM wrote the first draft of the article. VP, NA, AA, BM, DS and AG revised the initial article and provided critical input on methodology. All authors reviewed and approved the final version of the article.

Funding

None.

Conflict of interest statement

Vinay Prasad reports royalties from Johns Hopkins Press, Medscape, MedPage, consulting for UnitedHealthcare and speaking fees for eviCore. Vinay Prasad has a plenary session podcast that has Patreon backers. Vinay Prasad is funded to study low-value drugs through a grant from Arnold Ventures. The funder had no role in the design of this study. Aaron Goodman reports consulting for Seattle Genetics and EUSA Pharma. Douglas Sborov reports consulting for Janssen, SkylinDx, GlaxoSmithKline, Legend Biotech, Amgen and Celgene. None of the authors have any other conflicts of interest.

Acknowledgements

The authors acknowledge Dr Lee Wade for his assistance in developing a search strategy.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.07.036.

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