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# Is CAR T a drug or a therapeutic pathway? Intention to treat versus per protocol analysis of real world studies of CAR-T cell therapy in relapsed refractory diffuse large B cell lymphoma

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## ► To cite this version:

Rossana Di Staso, Beatrice Casadei, Frederick Locke, Michael D. Jain, Timothy Voorhees, et al.. Is CAR T a drug or a therapeutic pathway? Intention to treat versus per protocol analysis of real world studies of CAR-T cell therapy in relapsed refractory diffuse large B cell lymphoma. *Blood Cancer Journal*, 2024, 14 (1), pp.197. 10.1038/s41408-024-01183-8 . hal-04780223

**HAL Id: hal-04780223**

**<https://hal.science/hal-04780223v1>**

Submitted on 13 Nov 2024

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## CORRESPONDENCE OPEN



# Is CAR T a drug or a therapeutic pathway? Intention to treat versus per protocol analysis of real world studies of CAR-T cell therapy in relapsed refractory diffuse large B cell lymphoma

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*Blood Cancer Journal* (2024)14:197; <https://doi.org/10.1038/s41408-024-01183-8>

The rationale for this project arises from some considerations. Clinical trials often use surrogate endpoints (response rates) rather than direct measurement of benefit (survivals) as primary objective of the study. When both are considered, in clinical studies focusing on CAR T therapy in Hematology they are often estimated starting from infusion (analysis per protocol [PP]) and not from leukapheresis (analysis per intention-to-treat [ITT]) or in a modified ITT modality, i.e. counting only patients who achieved the infusion timepoint [1–4].

Studies on CAR T-cell therapy lend to possible biases when they do not consider patients who undergo leukapheresis but finally are not infused for a variety of competing risks (e.g., time of leukapheresis and enrollment, use of bridging therapy [BT], lymphodepleting regimens and, and in the near future, autologous versus allogeneic products, different standard of care clinical practice or patient populations). This makes difficult to perform a robust comparison of both the different available CAR T products and the drugs which share the same indication. Starting from these premises, real-world studies and national registries could be useful tools in determining a true PP versus ITT analysis as a mirror of the real benefit and feasibility of CAR T therapy if it is considered a therapeutic path, including competitive risks. As a consequence, to test our thesis, we conceived a project to provide a comprehensive overview of the benefits of CAR T-cell therapy in patients with relapsed/refractory (r/r) large B-cell lymphomas (LBCL) in the real-world setting recomputing results in both PP and ITT basis to show that both modalities bring useful information, and to propose a new CAR T analysis specific endpoint with a dedicated event-free survival (CAR T EFS) for assessment of the actual drug benefit and feasibility, also as a driver for future research.

To reach our aim, a systematic review was conducted for real-world studies on the effectiveness of anti-CD19 CAR T-cell products (axicabtagene ciloleucel and tisagenlecleucel) administered to r/r LBCL patients between 2017 (after first approval) and October 2022 (Supplementary Fig. S1). Researchers and cooperative groups worldwide ( $n=10$ ) provided original data and re-estimated endpoints in both PP and ITT modalities (taking into account also subjects who entering in the therapeutic journey with leukapheresis but finally did not undergo infusion) when lacking in the original research: overall and complete response rates (ORR, CRR), progression-free and overall survivals (PFS, OS) and duration of response (Table 1). We asked to estimate the new endpoint we defined, i.e. ITT CAR T EFS, starting from leukapheresis to patients' exit from therapeutic pathway due to any cause,

whatever happened first, also before infusion (date of decision to not infuse). Meta-analysis was performed on ORR and CRR separately in both ITT and PP populations with random-effect models.

For subgroup analyses with the help of metaregression, studies were categorized according to the CAR T product used, presence/absence of primary mediastinal B-cell lymphoma (PMBCL, 50%) patients and according to study location (5 in Europe versus 5 in USA). When Researchers shared the whole database, we performed also a pooled analysis, always preferable to meta-analysis because having individual patient data allows to create a homogeneous database and reduce bias. (ALMAIDEA 2022CUP:J33C22001420001).

Our analysis indicates that rates of patients who did not achieve the infusion timepoint ranged from 3.0% to 28.9%. As a consequence, ORR and CR rates change whether they are considered on ITT (ORR ranged from 34 to 76% and CRR from 21 to 59%, respectively) or on PP basis (ORR ranged from 35 to 82% and CRR from 29 to 64%, respectively). The rate of patients who received BT ranged in Europe between 78.7% to 87.0%, whereas in the USA it ranged between 50.0% to 58.0%. The 50% of studies did not record the exit date for subjects who finally did not receive CAR T-cell, reflecting the inability to calculate the ITT EFS. Three studies reported a median PP PFS shorter than the ITT PFS, and in all studies but one median PP OS was higher than ITT OS. Median DoR ranges from 20.2 months to not reached (Table 1). Meta-analyses comprise 2 246 patients for the ITT population and 1 988 patients for the PP population, with a 10% of not infused patients on average. Metanalyses for ITT ORR and CRR resulted in 57% (95% CI 48–66) and 38% (95% CI 31–46), respectively. The PP ORR and CRR were 68% (95% CI 57–77) and 45% (95% CI 37–53), respectively. For both rates in both populations, heterogeneity was never below 90% (Supplementary Table S1). Subgroup analysis showed a significant difference for CRR and ORR in both PP and ITT populations, with better results for studies conducted in USA which also reached a slightly lower heterogeneity that drops to 0.0% in the PP population (Supplementary Table S1; Fig. 1). The presence of PMBCL patients in study cohort did not impact significantly on response rates estimated in both PP and ITT modalities (Supplementary Table S1). The type of CAR T product chosen differed significantly between groups for CRR and ORR in the PP population. Axicabtagene ciloleucel (3 studies) and axicabtagene ciloleucel or tisagenlecleucel (6 studies) groups showed higher response rates compared to tisagenlecleucel (1 study). However considering only axicabtagene ciloleucel studies showed a decrease of heterogeneity for CRR (Supplementary Fig. S2). Meta-regressions did not indicate a statistically

Received: 30 July 2024 Revised: 23 October 2024 Accepted: 29 October 2024  
Published online: 07 November 2024

**Table 1.** Studies overview and pooled analysis.

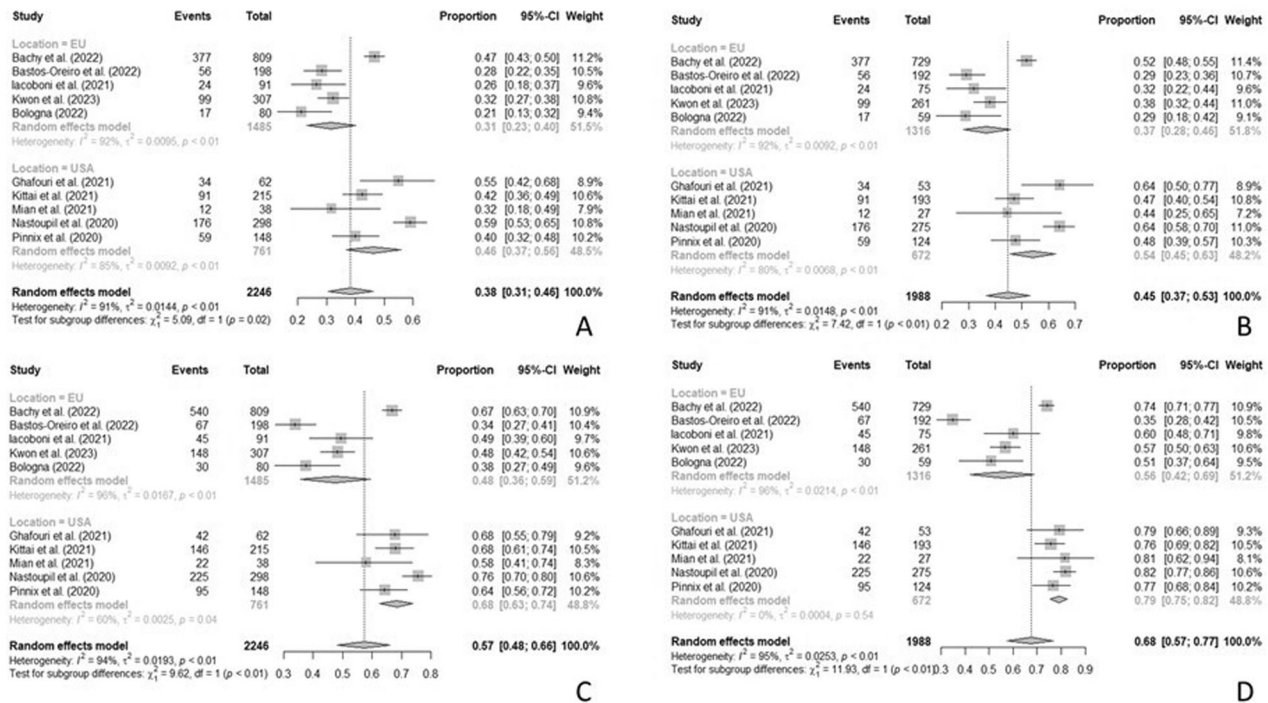
Study	Location	ITT Median follow up months (95%CI)	ITT Population N	Not infused patients %	PP population N	ORR_ITT (95%CI)	ORR_PP (95%CI)	CRR_ITT (95%CI)	CRR_PP (95%CI)	mPFS_ITT months (95%CI)	mPFS_PP months (95%CI)	mEFS_ITT months (95%CI)	mEFS_PP months (95%CI)	mOS_ITT months (95%CI)	mOS_PP months (95%CI)	mDoR months (95%CI)	BT %
Bachy et al. [6]	EU	13.1 (12.6–13.4)	809	9.9	729	67% (0.63–0.7)	74% (0.71–0.77)	47% (0.43–0.5)	52% (0.48–0.55)	NA	5.7 (4.1–7.5)	NA	NA	16.8 (13.3–21.6)	19 (NA)	11 (7.6–17.2)	78
Bastos-Oreiro et al. [7]	EU	11.0 (9–14)	198	3.0	192	34% (0.27–0.41)	35% (0.28–0.42)	28% (0.22–0.35)	29% (0.23–0.36)	5.1 (3.5–6.7)	5.6 (3.7–7.5)	5.1 (3.53–6.67)	3.3 (2.05–4.61)	14.5 (NA)	15 (NA)	6.4 (0.7–22)	82
Ghafari et al. [8] <sup>a</sup>	USA	39.5 (36.6–49.9)	62	14.5	53	68% (0.55–0.79)	79% (0.66–0.89)	55% (0.42–0.68)	64% (0.50–0.77)	5.57 (4–18.5)	6.67 (3.6–22.7)	5.23 (4–14.3)	6.67 (3.6–22.7)	11.1 (7.87–27.2)	17.7 (7.9–NR)	20.2 (10–31.9)	NA
Iacoboni et al. [9]	EU	9.7 (0.1–24.5)	91	17.6	75	49% (0.39–0.60)	60% (0.48–0.71)	26% (0.18–0.37)	32% (0.22–0.44)	4.6 (4.1–6.9)	3 (2.6–4.7)	NA	2.75 (1.2–4.3)	11.1 (7.9–NR)	10.7 (7.4–NR)	8.9 (2.2–NR)	87
Kittai et al. [10] <sup>b</sup>	USA	35.6 (29.9–41.7)	215	10.2	193	68% (0.61–0.74)	76% (0.69–0.82)	42% (0.36–0.49)	47% (0.40–0.54)	5.43 (4.23–7.53)	5.7 (3.57–10)	4.97 (3.97–6.83)	5.2 (3.3–9.2)	19.7 (12.9–38.3)	26.1 (15.5–NR)	15.1 (11.8–19.8)	NA
Kwon et al. [11]	EU	9.2 (8–11.5)	307	15.0	261	48% (0.42–0.54)	57% (0.50–0.62)	32% (0.27–0.38)	38% (0.32–0.44)	4.8 (4.5–5.6)	3.5 (3–6)	4.8 (4.5–5.6)	3.5 (3–6)	11.7 (12.9–38.3)	11.8 (1.3–31.4)	NR	80
Mian et al. [12]	USA	5.9 (4.5–10.8)	38	28.9	27	58% (0.41–0.74)	81% (0.62–0.94)	32% (0.18–0.49)	44% (0.25–0.65)	5.59 (4.3–NR)	9.07 (3.65–NR)	5.59 (4.3–NR)	9.07 (3.65–NR)	10.9 (6.08–NR)	13 (7.7–NR)	7.69 (2.73–NR)	50
Nastoupil et al. [13]	USA	13.8 (11.8–16.2)	298	7.7	275	76% (0.70–0.80)	82% (0.77–0.86)	59% (0.53–0.65)	64% (0.58–0.70)	7.16 (5.65–12.4)	8.31 (6.01–15.1)	NA	NA	NR	NR	NR	53
Pinnix et al. [14]	USA	11.1 (9.9–12.3)	148	16.2	124	64% (0.56–0.72)	77% (0.68–0.84)	40% (0.32–0.48)	48% (0.39–0.57)	4.8 (3.7–6.0)	6.2 (4.1–8.3)	NA	NA	16.7 (7.1–26.2)	21.9 (NA)	NA	50
Casadei et al. [15] <sup>a</sup>	EU	16 (13.8–21.8)	80	26.3	59	38% (0.27–0.49)	51% (0.37–0.64)	21% (0.13–0.32)	29% (0.18–0.42)	7.9 (6.23–14.9)	5.6 (3.07–16.5)	4.5 (3.77–7.47)	5.6 (3.07–16.5)	14.9 (13.4–NR)	17.2 (12.6–NR)	12.5 (5.1–NR)	80
Pooled analysis <sup>b</sup>		29.7 (25.3–32.8)	357	14.6	305	61% (0.56–0.66)	71% (0.66–0.76)	40% (0.35–0.45)	47% (0.41–0.53)	6.2 (4.9–7.9)	5.67 (4.1–8.33)	4.9 (4.1–6.2)	5.2 (3.97–7.07)	17.2 (13.4–26.6)	24.1 (16.2–33.1)	13.4 (10.9–18.9)	

BT values: re-estimations by the principal investigator of the project (LA) or new information provided by authors after request. In the other cells, data already present in the original publication.

BT bridging therapy, CRR complete response rate, ITT intention-to-treat, mDoR median duration of response, mEFS median event-free survival, mPFS median progression-free survival, mOS median overall survival, NA Not available, NR Not reached, ORR overall response rate, PP per protocol.

<sup>a</sup>Updated data.

<sup>b</sup>Ghafari et al. [8], Kittai et al. [10] and Casadei et al. [15].



**Fig. 1** Forest plot of the subgroup analysis according to study location was conducted. **A** CRR ITT; **B** CRR PP; **C** ORR ITT; **D** ORR PP. CRR complete response rate, ITT intention-to-treat, ORR overall response rate, PP per protocol.

significant influence of the different ratio of infused/not infused patients among studies, or of the different lengths of the median follow-up, this to the advantage of the robustness of the results. Of note, rate of patients who underwent BT had a significant influence on CRR of both PP and ITT populations ( $b = -0.635$ ;  $P = 0.034$  for ITT population and  $b = -0.850$ ;  $P = 0.006$  for PP population) and on ORR in PP population ( $b = -0.575$ ;  $P = 0.024$ ). The negative value of the coefficient  $b$  indicates that when the percentage of patients who underwent BT increase, the response rate decreases by about 60% (Supplementary Table S2 and Supplementary Fig. S3). At a median follow-up (ITT) of 29.7 months (95% CI 25.3–32.8), the pooled analysis led to an ITT ORR of 61% with a PP ORR of 71%. ITT CRR was 40% whereas the PP one resulted 47%, findings closer to those already published than those obtained with the meta-analysis. Median ITT OS resulted as 17.2 months while median PP OS was 24.1 months (Table 1). This rests on the fact that most patients who did not reach the infusion timepoint exited the CAR T pathway for death; moreover, infused subjects, included by definition in the PP analysis, may have taken advantage of further salvage treatments beyond CART. In contrast, both ITT and PP mPFS (6.2 versus 5.7 months) and mEFS (4.9 versus 5.2 months) were similar. PFS is slightly longer in the ITT population only as a consequence of the time elapsed between leukapheresis and infusion. This translates, de facto, into a non-significant difference between the two populations of patients, which points towards the reliability of PP PFS as a descriptor of CART effectiveness. On the other hand, an ITT mEFS lower than the PP mEFS, albeit without statistical significance, conveys the message that more dropout events have happened between leukapheresis and infusion. This means that more attention should be paid in terms of both patients' selection and patients management in this crucial period of the CAR T pathway.

The present research showed that limiting the analysis on the CAR T infused population alone could lead to a wrong choice of treatment as the response rates of the ITT population is also influenced by the percentage of people who undergo BT (with a proportion that do not achieve the infusion timepoint). The finding that the rate of patients who underwent BT negatively affects the response rate could be explained by a worse condition of patients needing BT to reach CAR T infusion; this effect on the response rate is present in both populations (ITT and PP). Another interesting result was that USA cohorts have a better response than those from Europe, and that the USA studies have a much lower heterogeneity compared to European ones confirming literature [5]. This could mean that higher heterogeneity in studies results could be better explained by substantial differences that may occur (e.g., timing of referral or leukapheresis, if and which BT is used, different lymphodepleting regimens or cellular product) in everyday clinical practice worldwide, also precluding a robust comparison among the different available CAR T products and the therapies which share the same indication.

This is the first study that analyzed and compared the benefit of CAR T-cell in real-world in both ITT and PP modalities on the same datasets, considering also patients who started CAR T pathway without reaching infusion timepoint. The importance of considering this new treatment option as a pathway should translate into implementation of CAR T patient registries that include the new endpoint we advocate for, i.e. ITT EFS, to establish population-level effectiveness of these products. In addition, there is also a need to improve the consistency of data collection requirements between countries (around 50% of the analyzed studies did not record the exit date due to any cause for subjects who finally did not receive CAR T-cell) and – ideally – to collect data at a cross-country level. Such collaboration increases the efficiency of data collection, quality of the evidence that is generated and a better management of the therapeutic pathway.



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## DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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## ACKNOWLEDGEMENTS

Funding was provided by Alma Mater Studiorum - University of Bologna (ID grant: ALMA IDEA 2022 CUP:J33C22001420001). We thank Massimo Agostini for data entry and AIL Bologna OdV (prot 2CSAIL21 Argnani).

## AUTHOR CONTRIBUTIONS

LA conceived and designed the study, wrote the paper and performed the analyses as principal biostatistician, collected the data, provided study materials, interpreted final results and approved the final manuscript. RM designed the study, edited the paper draft interpreted final results and approved the final manuscript. DG designed the study and edited the paper draft. RDS performed the analysis, wrote the paper, interpreted final results and approved the final manuscript. BC collected the data, provided study materials, interpreted final results and approved the final manuscript. FLL collected the data, provided study materials, interpreted final results and approved the final manuscript. MJ collected the data, provided study materials, interpreted final results and approved the final manuscript. TJV collected the data, provided study materials, interpreted final results and approved the final manuscript. ASK collected the data, provided study materials, interpreted final results and approved the final manuscript. MB collected the data, provided study materials, interpreted final results and approved the final manuscript. AG collected the data, provided study materials, interpreted final results and approved the final manuscript. AMG collected the data, provided study materials, interpreted final results and approved the final manuscript. MJT collected the data, provided study materials, interpreted final results and approved the final manuscript. MM collected the data, provided study materials, interpreted final results and approved the final manuscript. MJM collected the data, provided study materials, interpreted final results and approved the final manuscript. GI collected the data, provided study materials, interpreted final results and approved the final manuscript. PB collected the data, provided study materials, interpreted final results and approved the final manuscript. MK collected the data, provided study materials, interpreted final results and approved the final manuscript. RB collected the data, provided study materials, interpreted final results and approved the final manuscript. JLR collected the data, provided study materials, collected the data, provided study materials, interpreted final results and approved the final manuscript. AM collected the data, provided study materials, interpreted final results and approved the final manuscript. BH collected the data, provided study materials, interpreted final results and approved the final manuscript. EB collected the data, provided study materials, interpreted final results and approved the final manuscript. FM collected the data, provided study

materials, interpreted final results and approved the final manuscript. RH collected the data, provided study materials, interpreted final results and approved the final manuscript. CT collected the data, provided study materials, interpreted final results and approved the final manuscript. SLG collected the data, provided study materials, interpreted final results and approved the final manuscript. AB collected the data, provided study materials, interpreted final results and approved the final manuscript. PLZ collected the data, provided study materials, interpreted final results and approved the final manuscript.

### COMPETING INTERESTS

GI served as consultant and received honoraria from Novartis, Roche, Kite/Gilead, Bristol-Myers Squibb, Abbvie, Janssen, Sandoz, Miltenyi, AstraZeneca. PB as consultant and received honoraria from Allogene, Amgen, Autolus, BMS/Celgene, Kite/Gilead, Incyte, Miltenyi Biomedicine, Novartis, Nektar, Pfizer, Pierre Fabre. JLR served as consultant and received honoraria from Johnson&Johnson, Kite/Gilead, Novartis, BMS and Sanofi. RH served as consultant and received honoraria from Kite/Gilead, Novartis, Incyte, Janssen, MSD, Takeda, Roche, Bristol-Myers Squibb/Celgene, ADC Therapeutics, Incyte, Miltenyi. AMG served as consultant and received honoraria from Roche, BMS, Takeda, Janssen, Kyowa Kirin, Gilead/Kite, Incyte, Lilly, Miltenyi, Ideogen, Genmab, AbbVie, Sobi, AstraZeneca, GSK. MBO served as consultant and received honoraria from Roche, BMS, Novartis, Janssen, Kyowa Kirin, Gilead/Kite, Incyte, Lilly, Genmab, AbbVie, Sobi, AstraZeneca. The remaining authors declare no competing interests.

### ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Formal ethical approval was not needed as this is a secondary research and patient have already signed written informed consent for each study analyzed in the present manuscript.

### ADDITIONAL INFORMATION

**Supplementary information** The online version contains supplementary material available at <https://doi.org/10.1038/s41408-024-01183-8>.

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