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The academic point-of-care anti-CD19 chimeric antigen receptor T-cell product varnimcabtagene autoleucel (ARI-0001 cells) shows efficacy and safety in the treatment of relapsed/refractory B-cell non-Hodgkin lymphoma

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Summary
Varnimcabtagene autoleucel (var-cel) is an academic anti-CD19 chimeric antigen receptor (CAR) product used for the treatment of non-Hodgkin lymphoma (NHL) in the CART19-BE-01 trial. Here we report updated outcomes of patients with NHL treated with var-cel. B-cell recovery was compared with patients with acute lymphoblastic leukaemia (ALL). Forty-five patients with NHL were treated. Cytokine release syndrome (any grade) occurred in 84% of patients (4% grade ≥3) and neurotoxicity in 7% (2% grade ≥3). The objective response rate was 73% at Day +100, and the 3-year duration of response was 56%. The 3-year progression-free and overall survival were 40% and 52% respectively. High lactate dehydrogenase was the only covariate with

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an impact on progression-free survival. The 3-year incidence of B-cell recovery was lower in patients with NHL compared to ALL (25% vs. 60%). In conclusion, in patients with NHL, the toxicity of var-cel was manageable, while B-cell recovery was significantly prolonged compared to ALL. This trial was registered as NCT03144583.

KEYWORDS
CAR, CD19, NHL, var-cel

INTRODUCTION

Chimeric antigen receptor (CAR) T cells targeting CD19, such as tisagenlecleucel (tisa-cel),[1,2] axicabtagene ciloleucel (axi-cel),[3,4] lisocabtagene maraleucel (liso-cel)[5] and brexucabtagene autoleucel (brexu-cel),[6] have shown impressive results in patients with relapsed/refractory (R/R) B-cell non-Hodgkin lymphoma (NHL), leading to their approval in the European Union and other jurisdictions for the treatment of diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBL), transformed follicular lymphoma (tFL), mantle-cell lymphoma (MCL) and follicular lymphoma (FL). In addition, recent phase 3 data have led to extensions of indications for some of these products in patients with less advanced disease (first relapse in patients with DLBCL).[7,8] Of note, at the time of writing this paper, the only indications that are currently reimbursed in Spain are the original indications dating back to 2019 (DLBCL, PMBL and tFL after a minimum of two lines of therapy) at an approximate cost of €300 000.

In Spain, the results from the CART19-BE-01 clinical trial evaluating the safety and efficacy of the academic anti-CD19 CART-cell product varnimcabtagene autoleucel (var-cel, ARI-0001 cells) manufactured by Hospital Clínic de Barcelona (HCB),[9–11] led to its approval, as Hospital Exemption, by the Spanish Agency of Medicines (AEMPS) for patients older than 25 years of age with R/R acute lymphoblastic leukaemia (ALL).[12] The product's price was subsequently agreed upon with the Spanish Ministry of Health at €89 270. Furthermore, var-cel has been granted PRIority MEdicines designation by the European Medicines Agency for the same indication. Var-cel is not approved for the treatment of R/R NHL, but a name-based compassionate use may be requested for the same cost. These requests are individually approved by the AEMPS and a National Committee of Experts in CART-cell therapy. Patients with R/R NHL treated under compassionate use are those not covered by the approved indications of commercial CART-cell products.

Here we report the updated outcomes of all consecutive patients with R/R NHL treated with var-cel within the CART19-BE-01 clinical trial[9] and subsequent compassionate use.

MATERIALS AND METHODS

Patient population

This study includes all patients with CD19-positive R/R NHL treated with var-cel (ARI-0001 cells) at HCB from July 2017 to August 2022, including patients treated in the CART19-BE-01 trial (registered as NCT03144583) and the consecutive compassionate use.[9] The CART19-BE-01 study was a single-arm, multicentre open-label pilot study evaluating the safety and efficacy of var-cel in patients with R/R B-cell malignancies. However, patients with NHL were all treated at HCB. Eligible patients with NHL had to have all the following: (i) CD19-positive DLBCL, MCL or FL; (ii) age from 2 to 80 years; (iii) no macroscopic involvement of the central nervous system (CNS) at infusion, although CNS involvement that was controlled with intrathecal or systemic therapy prior to infusion was allowed; (iv) ECOG performance status 0–2; (v) estimated life expectancy from 3 months; and (vi) adequate venous access. Patients diagnosed with NHL were eligible if they were in second or further relapse and were either ineligible for, or had relapsed disease after, haematopoietic cell transplantation (HCT). Key exclusion criteria included history of other malignancy unless it had been in remission for more than 3 years; significant renal, hepatic, pulmonary or cardiac impairment; active immunosuppressive therapy; HIV infection; active HBV or HCV infection; and active infection requiring systemic therapy.

Patients with R/R NHL treated as compassionate use had the same inclusion/exclusion criteria but could suffer from other types of lymphoma (besides DLBCL, MCL or FL) provided that tumour cells were CD19-positive and the patients were not eligible for commercial CART-cell therapy available in Spain (axi-cel or tisa-cel). The AEMPS and the Institutional Review Board/Ethics Committee of HCB approved the trial, which were conducted in accordance with the principles of the Declaration of Helsinki (last updated version, Fortaleza, Brazil, 2013). Patients receiving var-cel as compassionate use are individually authorised by the AEMPS and the National Experts Committee. All patients provided informed consent in writing.

For the only purpose of evaluating var-cel persistence through B-cell recovery, adult patients with R/R ALL, whose outcomes have been reported elsewhere,[10] were compared to patients with R/R NHL.

Study design and end-points

The primary end-point of the CART19-BE-01 trial was safety as determined by the incidence of adverse events (AEs) and non-relapse mortality (NRM) at Day +100.[9] AEs of special interest were cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity

syndrome (ICANS). For this analysis, CRS and ICANS were graded according to the ASTCT 2019 consensus grading guidelines.[13] Other AEs were graded according to common terminology criteria, version 4.0. Efficacy was analysed using the Lugano criteria,[14] including bone marrow aspirate/biopsy and/or CSF analysis in cases of bone marrow and/or CNS involvement, as appropriate. Secondary end-points included objective and complete response rates (ORR/CRR), duration of response (DOR), progression-free survival (PFS), overall survival (OS) and cumulative incidence of B-cell recovery. The ORR/CRR was assessed at Day +28, Day +100, Month +6, Month +12 and Month +18, but the prespecified primary efficacy evaluation was performed at Day +100 from var-cel infusion. Vein-to-vein (V2V) time was defined from leukocytoapheresis to cell infusion.

Var-cel production, treatment and persistence

Following screening and confirmation of eligibility, patients were enrolled and underwent a mononuclear cell collection using Spectra Optia (Terumo BCT, Lakewood, CO, USA) or Amicus (Fresenius Kabi, Bad Homburg, Germany) blood separators. Var-cel was manufactured using the CliniMACS Prodigy system (Miltenyi) as previously described.[15,16] Cells were then transduced with a lentiviral vector containing the CAR gene construct, which comprises the single-chain variable fragment of the anti-CD19 A3B1 monoclonal antibody, a transmembrane CD8a domain, a 4-1BB intracellular costimulatory domain and a CD3z intracellular signalling domain. Following 6–11 days of expansion, depending on cell expansion, the cell product was washed, eluted, cryopreserved and tested for appearance, identity, purity, potency, sterility and adventitious agents.[15]

Before var-cel infusion, patients received fludarabine 30 mg/m^2/day plus cyclophosphamide 300 mg/m^2/day on Days −6, −5 and −4, followed by a target dose of 1–5 × 10^6 CAR+ cells/kg depending on the type of disease (5 × 10^6 CAR+ cells/kg for patients with predominantly lymphomatous disease and 1 × 10^6 CAR+ cells/kg for patients with predominantly leukaemic disease). The first three patients received a single intravenous infusion of var-cel on Day 0, whereas the remaining patients received the first fraction (10%) of var-cel on Day 0, followed by the second (30%) and third (60%) fractions separated at least by 24 h if there were no signs or symptoms of CRS/ICANS of macrophage activation syndrome. This amendment was motivated by three cases of lethal toxicity in the cohort of patients receiving a single intravenous infusion, all of whom were diagnosed with ALL.[9]

Var-cel persistence was measured as time to B-cell recovery (a minimum of two consecutive determinations showing the presence of B cells in peripheral blood). Human anti-mouse antibodies (HAMA) were measured as previously described.[9]

Statistical analysis

Response rates are presented with 95% exact Clopper-Pearson confidence intervals (CIs). NRM was calculated as a cumulative incidence from infusion, considering disease relapse as a competing event. DOR was calculated, for responding patients only, from Day +100 until disease progression, death or the last follow-up. PFS, OS and incidence of B-cell recovery were calculated from the day of infusion. All DOR, PFS and OS curves were plotted using the Kaplan–Meier method. B-cell recovery was computed as a cumulative incidence, considering death without B-cell recovery as a competing event. Univariate and multivariate analyses of factors with potential impact on PFS (indolent vs. aggressive; normal vs. high LDH; age; and dose administered) were performed using the log-rank test and Cox regression. Univariate and multivariate analysis of factors with potential impact on B-cell recovery (diagnosis, age and dose administered) was performed using Gray's test and Fine–Gray regression. Appropriate cut-off levels for cell dose and age were explored using maximally selected rank statistics. Statistical analyses were performed using R, version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). The CART19-BE-01 trial (EUDRA no 2016-2972-29) was registered at clinicaltrials.gov (NCT03144583).

RESULTS

Baseline characteristics

Ten patients with R/R NHL were enrolled in the CART19-BE-01 study and 41 in the subsequent compassionate use. Among these patients, 45 eventually received at least one dose of var-cel. The preliminary results obtained in patients included in the CART19-BE-01 trial[9] and in the first six patients with Richter transformation (RT)[17] have already been published. In two patients, a viable product could not be manufactured; three patients abandoned the programme because of rapidly progressing disease (one before and two after lymphodepletion chemotherapy, respectively); and one patient could not receive var-cel in April 2020 because of the COVID-19 pandemic and died of progressive disease (Figure 1). Table 1 displays the baseline characteristics of the entire patient population. Histology subtypes were classified as aggressive (DLBCL, tFL, PMBL, MCL, RT, high-grade lymphoma, grey-zone lymphoma, primary effusion lymphoma, primary CNS lymphoma and Burkitt lymphoma) and indolent (FL, splenic marginal zone lymphoma [MZL] and splenic diffuse red pulp B-cell lymphoma [SDRPBL]).

Besides the two patients who never received therapy due to manufacturing failure (two attempts), four additional patients required a second manufacturing procedure to secure a viable product (9% of all infused patients). The median age at inclusion in the CART-cell programme was 57 years (range, 19–74), with 25% of patients being older than 65 years.

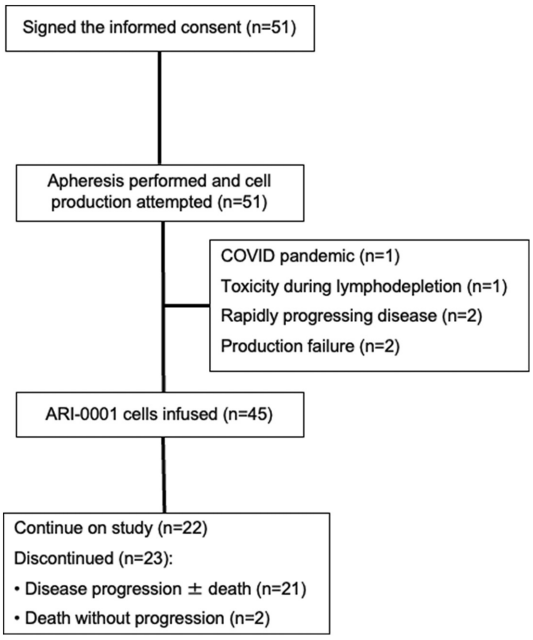

FIGURE 1 CONSORT diagram of patients with non-Hodgkin lymphoma included in the CART19-BE-01 trial and compassionate use programme.

The median of prior lines of therapy was 4 (range, 2–9). Moreover, 41 (80%) patients required bridging therapy while var-cel was manufactured (Table 2). Patients who eventually received therapy did so a median of 40 days (range, 23–195) after study inclusion (i.e. signature of informed consent) and 29 days (range, 18–182) after apheresis. Median cell production time was 8 (range, 6–11) days. Lymphodepleting chemotherapy was administered in an outpatient setting to 33 (72%) patients. The cut-off date for this analysis was January 2023. At that time, the median follow-up for survivors was 12.6 months (range, 3.9–44.6) from study inclusion.

Toxicity

The cumulative incidence of NRM was 0% at Day +100 and 7% at 3 years, accounting for two patients in total (both diagnosed with FL). The first patient died of pneumonia after a diagnosis of lung adenocarcinoma 13 months after a var-cel infusion. The second patient died of toxic epidermal necrolysis (TEN), which was diagnosed 2 weeks after var-cel infusion and was only partially responsive to corticosteroids. Repeated skin biopsies ruled out the presence of CART cells on the skin or any other causes. The patient eventually died of uncontrolled bacteraemia, in the context of active TEN, 5 months after therapy. Both patients died while in response (complete and partial, respectively), to their FL.

Regarding AEs of special interest, CRS (any grade) occurred in 38/45 infused patients (84%, 95% CI: 71–94), with a median onset time of 3 days (range, 0–6) and a median duration of 4 days (range, 0–13). There were two cases of grade ≥3 CRS (4%, 95% CI: 1–15) and three cases of ICANS (7%, 95% CI: 1–18), of which one was grade 3 (2%, 95% CI: 0–12). As a result of CRS, tocilizumab was administered to 13 patients (29%) with grades 1–3 CRS. Moreover, 14/42 patients received only one (6 patients) or two (8 patients) fractions of var-cel, as per protocol, because of significant CRS. Macrophage activation syndrome was documented in one patient (2%, 95% CI: 0–12). Grade ≥3 neutropenia was observed in 43 patients (96%, 95% CI: 85–99), with a median duration of 13 days (2–89). There were 18 cases (40%, 95% CI: 26–56) of grade ≥3 anaemia, and there were 24 cases (53%, 95% CI: 38–68) of grade ≥3 thrombocytopenia. granulocyte-colony-stimulating factor and eltrombopag support were needed, for the treatment of cytopenia, in 51% and 12% of patients respectively.

TABLE 1 Patients' baseline characteristics (intention-to-treat).

Characteristic	Patients ($n = 51$)
Disease type, *n* (%)	
Diffuse large B-cell lymphoma	5 (10)
Primary mediastinal large B-cell lymphoma	2 (4)
High-grade lymphoma	1 (2)
Grey-zone lymphoma	2 (4)
Primary effusion lymphoma	1 (2)
Transformed follicular lymphoma	1 (2)
Primary central nervous system B-cell lymphoma	2 (4)
Richter transformation	10 (20)
Burkitt lymphoma	3 (6)
Follicular lymphoma	12 (23)
Mantle-cell lymphoma	9 (17)
Marginal zone lymphoma	2 (4)
Splenic diffuse red pulp small B-cell lymphoma	1 (2)
Age, median (range)	57 (19–74)
Female sex, *n* (%)	22 (43)
Prior therapies, median (range)	4 (2–9)
Prior autologous haematopoietic cell transplantation, *n* (%)	18 (35)
Prior allogeneic haematopoietic cell transplantation, *n* (%)	8 (16)
High serum LDH, *n* (%)	29 (57)
History of bulky disease, *n* (%)	8 (16)
History of extra-nodal disease, *n* (%)	38 (75)
History of CNS disease, *n* (%)	9 (18)

Abbreviation: CNS, central nervous system.

Efficacy

The prespecified ORR (at Day +100) was 73% (95% CI: 58–85), with a CRR of 64% (95% CI: 49–78) for the entire population. The median DOR from response assessment (Day +100) had not been reached and was 56% (95% CI: 39–81) at 3 years. Median PFS from cell infusion was

TABLE 2 Outcomes during cell manufacturing and administration (intention-to-treat).

Characteristic	Patients ($n=51$)
Days from signature of CI to apheresis, median (range)	8 (2–48)
Days from signature of CI to infusion, median (range)	40 (23–195)
Days from apheresis to infusion (vein-to-vein time), median (range)	29 (18–182)
Days of cell production, median (range)	8 (6–11)
Successful productions, *n* (%)	
Two failed attempts (patient never infused)	2 (4)
One failed attempt, one successful production	4 (8)
Successful production in the first attempt	45 (88)
Starting material, *n* (%)	
Fresh mononuclear cells	47 (92)
Frozen mononuclear cells	4 (8)
Use of bridging therapy, *n* (%)	41 (80)
Type of bridging therapy, *n* (%)	
Cyclophosphamide	12 (29)
R-chemo combinations	8 (20)
Glucocorticoids alone	4 (10)
Ibrutinib and/or venetoclax	13 (32)
Radiotherapy	3 (7)
Intrathecal methotrexate	1 (2)
Administration of lymphodepleting chemotherapy, *n* (%) ($n=46$)[a]	
As inpatient	11 (24)
As outpatient	33 (72)
Both	2 (4)
CD3+ cells/microlitre of peripheral blood at the time of apheresis, median (range)	872 (100–9245)
Dose planned	
1×10^6 CAR+ cells/kg	2 (4)
5×10^6 CAR+ cells/kg	49 (96)
Type of administration, *n* (%) ($n=45$)	
Single dose	3 (7)
Fractionated (all 3 fractions administered)	28 (62)
Fractionated (2 fractions administered)	8 (18)
Fractionated (1 fraction administered)	6 (13)

[a]One patient received lymphodepleting chemotherapy but not varnimcabtagene autoleucel due to fast disease progression.

Abbreviation: CAR, chimeric antigen receptor.

10.4 months (95% CI: 6.48–not estimable) whereas median OS had not been reached. At 3 years, PFS and OS were estimated at 40% (95% CI: 26–61) and 52% (95% CI: 36–76) respectively. Responses, DOR, PFS and OS by histological subtypes are displayed in Table 3 and Figure 2A–C. The median cumulative incidence of B-cell recovery had not been reached and was estimated at 25% (95% CI: 12–38) at 3 years. The cumulative incidence of relapse/progression was 53% at 3 years (95% CI: 37–71). Of 21 cases of disease relapse/progression after cell infusion, 3 (14%) were CD19-negative, all of them in patients with RT. Table 4 shows these outcomes for CART19-BE-01 and compassionate use patients separately.

Univariate analysis revealed that both histology (indolent vs. aggressive) and serum LDH (normal vs. high) had an impact on PFS. Patients with indolent disease (FL, MZL and SDRPBL) had not reached their median PFS, whereas patients with aggressive histology had a median PFS of 6.7 months (95% CI: 4.3–not estimable). Moreover, patients with high serum LDH had a shorter median PFS (6.1 months) compared to those with normal LDH (median not reached).

Var-cel persistence

To contextualise the results of CART-cell persistence, as measured by the incidence of B-cell recovery, we evaluated 134 adult patients treated with var-cel at our institution. We observed a significantly lower incidence of B-cell recovery in patients with NHL compared to ALL (25% vs. 60% at 3 years, Figure 2D). Since the dose administered was different (maximum dose of 1×10^6 CAR+ cells/kg for ALL vs. 5×10^6 CAR+ cells/kg for NHL, depending on tolerability), we also explored whether the var-cel dose was associated with B-cell recovery, but there was no association. We also investigated the impact of age, since patients with ALL were significantly younger than those diagnosed with NHL. Of note, patients younger than 30 years of age had a 62% probability of B-cell recovery at 3 years compared to older patients (41%). HAMA were detected in 49% and 35% of patients with ALL and NHL respectively.

DISCUSSION

In this paper, we present the results obtained with varnimcabtagene autoleucel in patients with R/R NHL. With a few exceptions, all occurring in earlier phases of our development (2017–2018), patients treated with var-cel suffered from disease subtypes that were (and still are) not eligible for commercial CART-cell products in Spain (e.g. MCL, FL and RT). This is a population of heavily pretreated patients, with a median of 4 prior lines of therapy and prior autologous and allogeneic HCT in 35% and 16% respectively. Moreover, a high proportion (80%) of patients required bridging therapy during cell manufacturing to control a rapidly proliferating disease. This is comparable to most pivotal trials of CART cells for the treatment of NHL.[1–6]

One of the advantages of this programme is the relatively short median time from enrolment to infusion (40 days) and time from apheresis to infusion (vein-to-vein time, 29 days). These numbers show an improvement compared to the patients originally treated at the CART19-BE-01

TABLE 3 Efficacy of varnimcabtagene autoleucel according to disease histology (infused patients only).

Subtype	ORR at Day +100, % (95% CI)	CRR at Day +100, % (95% CI)	DOR at 3 years, % (95% CI)	PFS at 3 years, % (95% CI)	OS at 3 years, % (95% CI)
Aggressive NHL					
DLBCL, PMBL and tFL ($n=7$)	57 (18–90)	43 (10–81)	25 (46–100)	14 (2–88)	14 (2–88)
Richter transformation ($n=9$)	56 (21–86)	44 (14–79)	80 (52–100)	44 (21–92)	56 (31–99)
Mantle-cell lymphoma ($n=7$)	86 (42–99)	86 (42–99)	67 (30–100)	56 (23–100)	67 (30–100)
Other (HGL, GZL, PEL, PCNSL, BL) ($n=8$)	63 (24–91)	63 (24–91)	40 (14–100)	19 (4–98)	75 (50–100)
Indolent NHL					
Follicular lymphoma ($n=11$)	100 (72–100)	82 (48–98)	62 (35–100)	62 (35–100)	72 (44–100)
Other (MZL, SDRPBL) ($n=3$)	67 (9–99)	67 (9–99)	NE	67 (30–100)	50 (13–100)

Abbreviations: BL, Burkitt lymphoma; CI, confidence interval; CRR, complete response rate; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; GZL, grey-zone lymphoma; HGL, high-grade lymphoma; MZL, marginal zone lymphoma; NE, not estimable; NHL, non-Hodgkin lymphoma; ORR, objective response rate; OS, overall survival; PCNSL, primary central nervous system lymphoma; PEL, primary effusion lymphoma; PFS, progression-free survival; PMBL, primary mediastinal B-cell lymphoma; SDRPBL, splenic diffuse red pulp B-cell lymphoma; tFL, transformed follicular lymphoma.

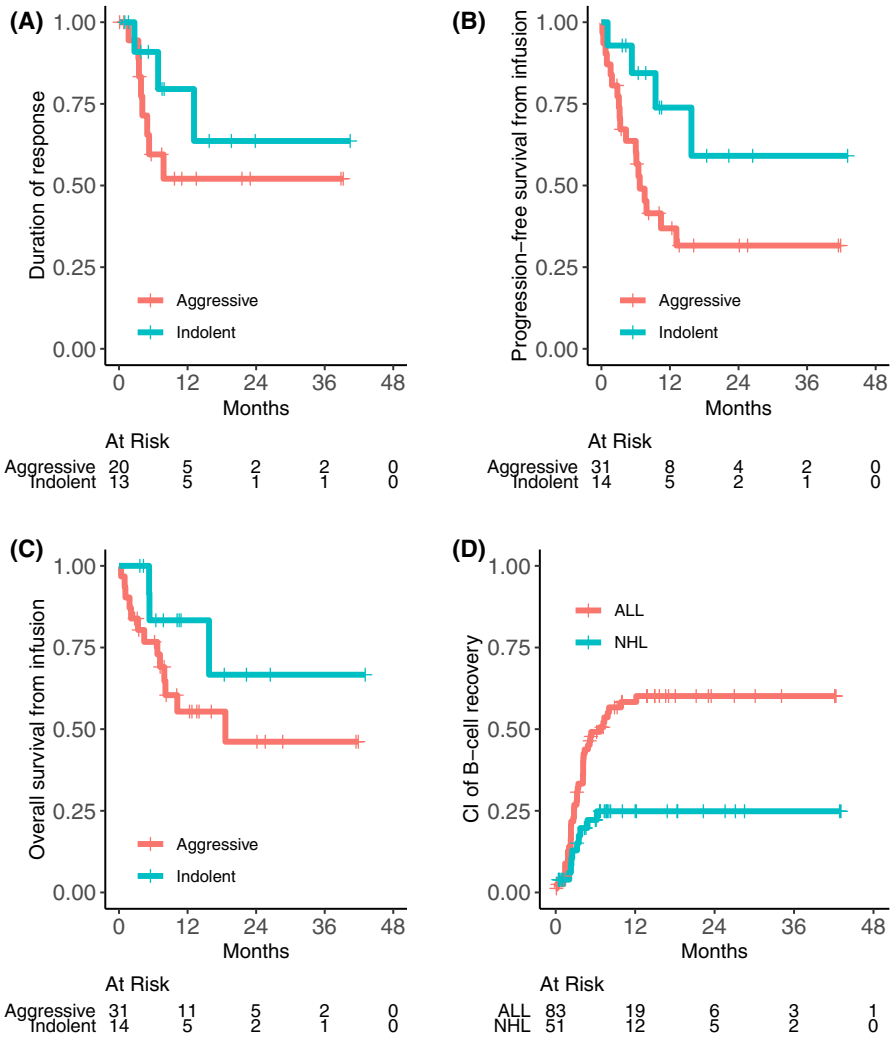

FIGURE 2 Duration of response from evaluation (Day +100) (A); progression-free survival from cell infusion (B); overall survival from cell infusion (C) according to disease histology (aggressive vs. indolent). Panel (D) displays the cumulative incidence of B-cell recovery for patients with non-Hodgkin lymphoma (all subtypes) compared to those with acute lymphoblastic leukaemia.

trial (54 and 42 days respectively),[9] reflecting a reduced incidence of failed/repeated productions over time and improved coordination between our centre and other referring institutions across the country. Another advantage of our product is its manageable safety profile, with grade ≥3 CRS and ICANS documented in 4% and 2% of

TABLE 4 Efficacy of varnimcabtagene autoleucel according to type of administration (CART19-BE-01 trial vs. compassionate use programme).

Outcome	CART19-BE-01 trial ($n = 8$)	Compassionate use programme ($n = 37$)
ORR at Day +100, % (95% CI)	75 (35–97)	73 (56–86)
CRR at Day +100, % (95% CI)	50 (16–84)	68 (50–82)
DOR at 3 years, % (95% CI)	50 (23–100)	57 (37–88)
PFS at 3 years, % (95% CI)	38 (15–92)	39 (23–65)
OS at 3 years, % (95% CI)	38 (15–92)	59 (41–85)

Abbreviations: CI, confidence interval; CRR, complete response rate; DOR, duration of response; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

patients, respectively, and a very low admission rate to the intensive care unit. These rates are comparable to those obtained with liso-cel,[5] tisa-cel,[1,2] axi-cel[3,4] and brexu-cel[6] in similar patient populations, which is remarkable considering that the median dose administered to patients is significantly higher (5×10^6 CAR+ cells/kg). We believe this is the result of a more liberal use of tocilizumab (29% of patients) as currently recommended in most guidelines,[13,18] but more importantly, to the fractionated administration of our product, which significantly reduced the incidence of grade ≥3 CRS from 27% to 4% in patients with R/R ALL.[9] Of note, our anti-BCMA product (ARI0002h) is also administered in fractions, and the incidences of grade ≥3 CRS/ICANS are equally low.[19]

With the reduction in the incidence of severe CRS/ICANS, persistent cytopenia is becoming one of the major complications of CART-cell therapy,[20] and patients treated with var-cel are no exception. However, judicious use of drugs such as G-CSF and eltrombopag and the existence of a well-established at-home hospitalisation programme at our institution have facilitated the management of this complication in the outpatient setting. Moreover, and in contrast with patients with R/R ALL who usually are severely neutropenic at the time of treatment initiation, most (72%) patients with R/R NHL receiving var-cel therapy received lymphodepletion chemotherapy in the outpatient setting as well, which significantly reduced the number of days of hospitalisation and patient burden.

It is difficult to draw definitive conclusions from our study in view of the various histological entities included. However, we have confirmed a phenomenon already identified with other CART-cell products[21–23]: the value of serum LDH as a potential predictive biomarker in patients with R/R NHL treated with CART-cell therapy. In our study, patients with high LDH had a significantly shorter PFS compared to patients with normal LDH levels, and this effect was independent from tumour histology. This finding might highlight the importance of achieving the best possible disease control prior to var-cel infusion to optimise the results of these immune therapies.

Unexpectedly, the cumulative incidence of B-cell recovery was lower for patients with R/R NHL compared to those with R/R ALL. Of note, the opposite phenomenon was observed when tisa-cel was used to treat paediatric patients with ALL (median time to B-cell recovery of 35 months)[24] or adult patients with NHL (median time to B-cell recovery of 7 months).[25] Considering that patients with R/R NHL treated with var-cel were older than those diagnosed with R/R ALL (even after excluding paediatric patients from the analysis) and that the median var-cel dose administered to patients with R/R NHL was five times higher, we are unsure about the contribution of each of these factors (age vs. dose vs. disease). Additionally, we found a trend towards a higher occurrence of HAMA in patients with ALL (49% vs. 35%), but the reasons behind this fact are unclear.

The limitations of this study are numerous and include the heterogeneity of the patient population and the post hoc statistical analysis. However, all patients were uniformly managed in the same institution, and their inclusion in the programme was collectively discussed at multidisciplinary meetings. Moreover, response to therapy was independently assessed by two specialists following consensus guidelines.

In conclusion, we have presented the results obtained with var-cel in patients with R/R NHL, mostly in indications where commercial CART-cell products are not reimbursed in Spain. Despite the histological heterogeneity, we believe that var-cel holds promise for the treatment of adult patients with R/R NHL, particularly in the case of indolent malignancies. Moreover, the toxicity of the product was manageable, both manufacturing and hospital admission times could be shortened, and the product was 3–4 times cheaper than axi-cel or tisa-cel, which reduced the burden for patients, families, healthcare providers and payers.

AUTHOR CONTRIBUTIONS

Núria Martínez-Cibrián, Manel Juan and Julio Delgado wrote the paper; Núria Martínez-Cibrián, Valentín Ortiz-Maldonado, Eva Giné, Armando López-Guillermo, Carlos Fernández de Larrea and Álvaro Urbano-Ispizua provided significant contributions to the study analysis; Núria Martínez-Cibrián, Valentín Ortiz-Maldonado, Marta Español-Rego, Leticia Alserawan, Helena Brillembourg and Andrea Blázquez collected data; Núria Martínez-Cibrián, Valentín Ortiz-Maldonado, Laura Magnano, Eva Giné, Juan G. Correa, Pablo Mozas, Luis Gerardo Rodríguez-Lobato, Andrea Rivero, Mercedes Montoro-Lorite, Pilar Ayora, Helena Brillembourg, Armando López-Guillermo and Julio Delgado looked after the patients; Marta Español-Rego, Sergio Navarro, Leticia Alserawan, E. Azucena González-Navarro, María Sánchez-Castañón, Raquel Cabezón, Daniel Benítez-Ribas and Mariona Pascal manufactured var-cel, monitored B-cell aplasia/recovery and HAMA, and were responsible for quality control tests; Maria Castellà and Manel Juan designed the CAR construct and produced the vectors; Xavier Setoaín and Sonia Rodríguez assessed imaging studies before and after therapy; Joan Cid and Miquel Lozano performed leukocytaphereses; Julio Delgado performed the statistical analysis; Eulalia Olesti, Sara Varea, Elena Guillén and Joaquín Sáez-Peñataro coordinated data collection,

document preparation and pharmacovigilance. Valentín Ortiz-Maldonado, Sara Varea, Mariona Pascal, Álvaro Urbano-Ispizua, Manel Juan and Julio Delgado coordinated the entire CART-cell programme. All authors reviewed and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

NM-C: honoraria and travel grants (Kite Gilead). VO-M: consultancy (Kite Gilead, Celgene-BMS, Miltenyi, Pfizer, Novartis and Janssen); honoraria (Kite Gilead, Celgene-BMS and Janssen); travel grants (Kite, Celgene-BMS, Novartis, Roche, Takeda and Janssen). EGi: consultancy (Kite Gilead, Janssen and Roche); research funding (Kite Gilead, Janssen and Roche). JGC: honoraria and travel grants (Astra Zeneca, Janssen and Abbvie). LGR-L: honoraria and travel grants (Janssen, Amgen, BMS, GSK and Sanofi). CFdL: consultancy and honoraria (GSK, Sanofi, BeiGene, Amgen, BMS and Janssen); honoraria (Pfizer); research funding (GSK, Amgen and Janssen). ALG: consultancy (Roche, Kite Gilead, Genmab, Celgene and Abbvie); research funding (Kite Gilead and Roche); honoraria (Kite Gilead and Roche). MJ: consultancy (Kite Gilead and Grifols); honoraria (Kite Gilead and Grifols). ME-R, AB, JC, ML, LM, PM, AR, MM-L, PA, ML, SN, LA, EAG-N, MC, MS-C, RC, DB-R, XS, SR, HB, SV, EO, EGu, JS-P, MP, AU-I and JD have no competing interests to declare besides being employed by HCB, the non-profit institution that manufactures varnimcabtagene autoleucel.

DATA AVAILABILITY STATEMENT

The data used for this report are available upon reasonable request.

ETHICS STATEMENT

The AEMPS and the Institutional Review Board/Ethics Committee of HCB approved the trial, which were conducted in accordance with the principles of the Declaration of Helsinki (last updated version, Fortaleza, Brazil, 2013). Patients receiving var-cel as compassionate use are individually authorised by the AEMPS and the National Experts Committee.

PATIENT CONSENT STATEMENT

All patients provided informed consent in writing.

CLINICAL TRIAL REGISTRATION

This trial was registered at clinicaltrials.gov as NCT03144583.

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REFERENCES

1. Schuster SJ, Bishop MR, Tam CS, Waller EK, Borchmann P, McGuirk JP, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2019;380:45–56.
2. Fowler NH, Dickinson M, Dreyling M, Martinez-Lopez J, Kolstad A, Butler J, et al. Tisagenlecleucel in adult relapsed or refractory follicular lymphoma: the phase 2 ELARA trial. Nat Med. 2022;28:325–32.
3. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017;377:2531–44.
4. Jacobson CA, Chavez JC, Sehgal AR, William BM, Munoz J, Salles G, et al. Axicabtagene ciloleucel in relapsed or refractory indolent non-Hodgkin lymphoma (ZUMA-5): a single-arm, multicentre, phase 2 trial. Lancet Oncol. 2022;23:91–103.
5. Abramson JS, Palomba ML, Gordon LI, Lunning MA, Wang M, Arnason J, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet. 2020;396:839–52.
6. Wang M, Munoz J, Goy A, Locke FL, Jacobson CA, Hill BT, et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. N Engl J Med. 2020;382:1331–42.
7. Locke FL, Miklos DB, Jacobson CA, Perales M-A, Kersten M-J, Oluwole OO, et al. Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma. N Engl J Med. 2022;386:640–54.
8. Kamdar M, Solomon SR, Arnason J, Johnston PB, Glass B, Bachanova V, et al. Lisocabtagene maraleucel versus standard of care with salvage chemotherapy followed by autologous stem cell transplantation as second-line treatment in patients with relapsed or refractory large

B-cell lymphoma (TRANSFORM): results from an interim analysis of an open-label, randomised, phase 3 trial. Lancet. 2022;399:2294–308.
9. Ortíz-Maldonado V, Rives S, Castellà M, Alonso-Saladrigues A, Benítez-Ribas D, Caballero-Baños M, et al. CART19-BE-01: a multicenter trial of ARI-0001 cell therapy in patients with CD19+ relapsed/refractory malignancies. Mol Ther. 2021;29:636–44.
10. Ortiz-Maldonado V, Rives S, Español-Rego M, Alonso-Saladrigues A, Montoro M, Magnano L, et al. Factors associated with the clinical outcome of patients with relapsed/refractory CD19+ acute lymphoblastic leukemia treated with ARI-0001 CART19-cell therapy. J Immunother Cancer. 2021;9:e003644.
11. Ortiz-Maldonado V, Alonso-Saladrigues A, Español-Rego M, Martínez-Cibrián N, Faura A, Magnano L, et al. Results of ARI-0001 CART19 cell therapy in patients with relapsed/refractory CD19-positive acute lymphoblastic leukemia with isolated extramedullary disease. Am J Hematol. 2022;97:731–9.
12. Juan M, Delgado J, Calvo G, Trias E, Urbano-Ispizua A. Is hospital exemption an alternative or a bridge to European Medicines Agency for developing academic chimeric antigen receptor T-cell in Europe? Our experience with ARI-0001. Hum Gene Ther. 2021;32:1004–7.
13. Lee DW, Santomasso BD, Locke FL, Ghobadi A, Turtle CJ, Brudno JN, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019;25:625–38.
14. Alvarnas JC, Brown PA, Aoun P, Ballen KK, Barta SK, Borate U, et al. Acute lymphoblastic leukemia, version 2.2015: clinical practice guidelines in oncology. J Natl Compr Cancer Netw. 2015;13:1240–79.
15. Castella M, Boronat A, Martín-Ibáñez R, Rodríguez V, Suñé G, Caballero M, et al. Development of a novel anti-CD19 chimeric antigen receptor: a paradigm for an affordable CAR T cell production at academic institutions. Mol Ther Methods Clin Dev. 2019;12:134–44.
16. Castella M, Caballero-Baños M, Ortiz-Maldonado V, González-Navarro EA, Suñé G, Antoñana A, et al. Point-of-care CAR T-cell production (ARI-0001) using a closed semi-automatic bioreactor: experience from an academic phase I clinical trial. Front Immunol. 2020;11:482.
17. Ortiz-Maldonado V, Frigola G, Español-Rego M, Balagué O, Martínez-Cibrián N, Magnano L, et al. Results of ARI-0001 CART19 cells in patients with chronic lymphocytic leukemia and Richter's transformation. Front Oncol. 2022;12:828471.
18. Schneider BJ, Naidoo J, Santomasso BD, Lacchetti C, Adkins S, Anadkat M, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. J Clin Oncol. 2021;39:4073–126.
19. Oliver-Caldés A, González-Calle V, Cabañas V, Español-Rego M, Rodríguez-Otero P, Reguera JL, et al. Fractionated initial infusion and booster dose of ARI0002h, a humanised, BCMA-directed CAR T-cell therapy, for patients with relapsed or refractory multiple myeloma (CARTBCMA-HCB-01): a single-arm, multicentre, academic pilot study. Lancet Oncol. 2023;24:913–24.
20. Rejeski K, Subklewe M, Aljurf M, Bachy E, Balduzzi AC, Barba P, et al. Immune effector cell-associated Hematotoxicity (ICAHT): EHA/EBMT consensus grading and best practice recommendations. Blood. 2023;142:865–77. https://doi.org/10.1182/BLOOD.2023020578
21. Nastoupil LJ, Jain MD, Feng L, Spiegel JY, Ghobadi A, Lin Y, et al. Standard-of-care axicabtagene ciloleucel for relapsed or refractory large B-cell lymphoma: results from the US Lymphoma CAR T Consortium. J Clin Oncol. 2020;38:3119–28.
22. Shouval R, Tomas AA, Fein JA, Flynn JR, Markovits E, Mayer S, et al. Impact of TP53 genomic alterations in large B-cell lymphoma treated with CD19-chimeric antigen receptor T-cell therapy. J Clin Oncol. 2022;40:369–81.
23. Hirayama AV, Gauthier J, Hay KA, Voutsinas JM, Wu Q, Pender BS, et al. High rate of durable complete remission in follicular lymphoma after CD19 CAR-T cell immunotherapy. Blood. 2019;134:636–40.
24. Laetsch TW, Maude SL, Rives S, Hiramatsu H, Bittencourt H, Bader P, et al. Three-year update of tisagenlecleucel in pediatric and young adult patients with relapsed/refractory acute lymphoblastic leukemia in the ELIANA trial. J Clin Oncol. 2023;41:1664–9.
25. Schuster SJ, Svoboda J, Chong EA, Nasta SD, Mato AR, Anak Ö, et al. Chimeric antigen receptor T cells in refractory B-cell lymphomas. N Engl J Med. 2017;377:2545–54.

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