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RESEARCH ARTICLE

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Results of ARI-0001 CART19 cell therapy in patients with relapsed/refractory CD19-positive acute lymphoblastic leukemia with isolated extramedullary disease

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Abstract

We evaluated outcomes of 18 patients with isolated extramedullary disease (iEMD) relapsed/refractory (R/R) B-cell acute lymphoblastic leukemia (B-ALL) treated with the CD19-directed CAR T cells ARI-0001 in two centers (adult and pediatric), including patients treated in the CART19-BE-01 trial and the consecutive compassionate use program. iEMD was detected by PET-CT in 78% (14/18), and/or by cerebrospinal fluid analysis in 28% (5/18). Patients received cyclophosphamide and fludarabine followed by

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1×10^6 ARI-0001 cells/kg, initially as a single dose (first patient) and later split into three fractions (10%, 30%, and 60%). Cytokine release syndrome (CRS) occurred in 50% (9/18) of patients, with no cases of grade ≥3 CRS, and 1 case (6%) of grade 1 neurotoxicity. Tocilizumab was used in 6% of patients (1/18). Procedure-related mortality was 0% at 2 years. Objective responses were seen in 94% (95% confidence interval [CI]: 73%–99%) of patients, with complete responses (CR) seen in 78% (95% CI: 52%–94%) of them. Progression-free and overall survival were 49% (95% CI: 30%–79%) and 61% (95% CI: 40%–92%) at 2 years. In conclusion, the use of ARI-0001 cells in patients with R/R ALL and iEMD was associated with a safety and efficacy profile that is comparable with what is observed in patients with marrow involvement and in line with other CART19 products.

1 | INTRODUCTION

Several academic and commercial chimeric antigen receptor T cell products targeting CD19 (CART19) have achieved complete response (CR) rates of 60%–85% in patients with CD19-positive relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL).[1–12] Patients with isolated extramedullary disease (iEMD) have been systematically excluded from most CART19 clinical trials performed to date, including the pivotal trial for the only commercially available product,[2] probably due to the lack of consensus in the evaluation of response to therapy in these patients as well as concerns about poor efficacy and increased risk of neurotoxicity in individuals with central nervous system (CNS) disease. Consequently, data on safety and efficacy of CART19 therapy in patients with R/R ALL and iEMD remain scarce even though iEMD is particularly frequent in patients with relapsed disease after allogeneic hematopoietic cell transplantation (alloHCT)[13] or blinatumomab.[14]

The prognosis of patients who present with iEMD is controversial. Generally speaking, they have a better prognosis compared to those with blood and marrow disease, particularly in the pediatric population.[15] On the other hand, tumor cells from patients with iEMD are biologically different from those from patients with blood or bone marrow disease,[16] and probably possess a special ability to escape the immune-vigilance provided by T-cells. Indeed, the graft versus leukemia effect conferred by alloHCT appears less effective for EMD compared to blood or bone marrow disease in some series, but not in others.[17,18] The results in small series of patients treated with CART19 cells are contradictory, but mostly revealing a worse outcome for patients with EMD.[19–27]

Here we report the outcomes of all consecutive patients with R/R B-ALL and iEMD treated with ARI-0001 cells within the CART19-BE-01 clinical trial[4] and subsequent compassionate use program (CUP).

2 | PATIENTS AND METHODS

2.1 | Patient population

This study includes all patients with CD19-positive R/R ALL treated with ARI-0001 cells in two centers (Hospital Clinic of Barcelona for adults and Hospital Sant Joan de Déu of Barcelona for pediatrics) from January 2019 to September 2021, including patients treated in the CART19-BE-01 trial (trial registered as ClinicalTrials.gov: NCT03144583) and the consecutive CUP.[4,28] The CART19-BE-01 study was a single-arm, multicenter, open-label pilot study evaluating the safety and efficacy of ARI-0001 cells (Figure 1) in patients with R/R B-cell malignancies. Eligible patients with ALL had to have all the following: (1) CD19-positive disease; (2) age from 2 to 80 years; (3) no CNS-3 involvement at infusion, although CNS-2 or CNS-3 that was controlled with intrathecal or systemic therapy prior to infusion was allowed (4) ECOG performance status 0–2; (5) estimated life expectancy from 3 months; and (6) adequate venous access. Patients were eligible if they suffered from ALL in second relapse or higher, or refractory to at least 2 lines of therapy, either ineligible for or with relapsed disease after alloHCT. Key exclusion criteria included history of other malignancy unless it had been in remission for more than 3 years; severe renal, hepatic, pulmonary, or cardiac impairment; active immunosuppressive therapy; HIV infection; active HBV or HCV infection; and active infection requiring systemic therapy. All patients provided written, informed consent. The Spanish Agency of Medicines and Sanitary Products (AEMPS) and Institutional Review Boards/Ethics Committees of each study site approved the trial and the CUP, which were conducted in accordance with the principles of the Declaration of Helsinki (last updated version, Fortaleza, Brazil, 2013).

For the purpose of this analysis, patients were selected if, at study inclusion, they had detectable disease in the cerebrospinal fluid (CSF)

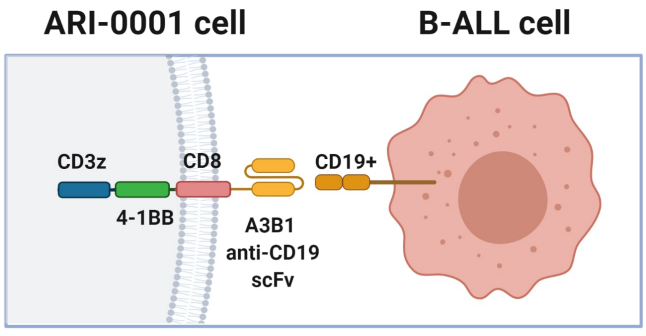

FIGURE 1 Diagram of ARI-0001 cells depicting the construct and the interaction of the CAR with the tumor cell [Color figure can be viewed at wileyonlinelibrary.com]

or by imaging studies and normal peripheral blood and bone marrow (less than 5% of blasts by morphology and negative measurable residual disease [MRD] by flow cytometry, with a minimum sensitivity of 0.01%).

TABLE 1 Baseline characteristics of patients included in this study

Characteristic	$n = 18$
Age (year), median (range)	27 (8–68)
Female sex, *n* (%)	5 (28%)
Abnormal cytogenetics, *n* (%)	12 (67%)
pH chromosome [t(9;22)]	2 (11%)
t(12;21)	2 (11%)
t(1;19)	1 (5%)
pH-like (CRLF2 rearrangement)	1 (5%)
t(8;14)	1 (5%)
Other	5 (28%)
Blast count in bone marrow at screening, median (range)	1% (0–4%)
Prior lines of therapy, median (range)	4.5 (2–6)
Prior blinatumomab, *n* (%)	6 (33%)
Prior inotuzumab ozogamicin, *n* (%)	9 (50%)
Prior allogeneic hematopoietic cell transplantation, *n* (%)	16 (89%)
Bridging chemotherapy[a], *n* (%)	15 (83%)
Maintenance-like (e.g., 6-mercaptopurine, methotrexate)	5 (28%)
Intrathecal chemotherapy	3 (17%)
Tyrosine kinase inhibitors (dasatinib, ponatinib)	2 (11%)
Radiotherapy	2 (11%)
Inotuzumab ozogamicin	1 (5%)
Blinatumomab	1 (5%)
Intensive chemotherapy	8 (44%)
Extramedullary disease at screening[a], *n* (%)	18 (100%)
Bone	7 (39%)
Cerebrospinal fluid	5 (28%)
Lymphadenopathy	3 (17%)
Breast	3 (17%)
Soft tissue	3 (17%)
Paranasal sinuses	2 (11%)
Muscle	2 (11%)
Mediastinum	2 (11%)
Lung	1 (6%)
Liver	1 (6%)
Stomach	1 (6%)
Pancreas	1 (6%)
Skin	1 (6%)

[a]Some patients received more than one bridging therapy or had more than one extramedullary location and therefore the percentages do not sum 100%.

2.2 | Study design and endpoints

The primary endpoint of the CART19-BE-01 trial was safety as determined by procedure-related mortality (PRM) at day +100.[4] Adverse events (AEs) of special interest were cytokine release syndrome (CRS) and immune-effector cell associated neurotoxicity syndrome (ICANS). Other AEs were retrospectively graded

TABLE 2 Adverse events of special interest or registered in >10% of patients included in this study

Adverse event	All grades, *n* (%)	Grade ≥ 3, *n* (%)
Lymphopenia	16 (89)	16 (89)
Hypogammaglobulinemia	16 (89)	0 (0)
Neutropenia	15 (83)	15 (83)
Anemia	12 (67)	1 (6)
Thrombocytopenia	11 (61)	7 (39)
Cytokine release syndrome	9 (50)	0 (0)
Increased AST	6 (33)	0 (0)
Increased ALT	6 (33)	1 (6)
Skin rash	6 (33)	1 (6)
Viral infection	5 (28)	1 (6)
Pyrexia	5 (28)	1 (6)
Increased GGT	4 (22)	1 (6)
Febrile neutropenia	4 (22)	3 (17)
Headache	4 (22)	0 (0)
Bronchitis	4 (22)	1 (6)
Increased alkaline phosphatase	3 (17)	0 (0)
Vomiting	3 (17)	0 (0)
Arthralgia	3 (17)	0 (0)
Peripheral edema	3 (17)	0 (0)
Dysgeusia	3 (17)	0 (0)
Water intoxication	3 (17)	0 (0)
Bacteremia	3 (17)	2 (11)
Pneumonia	2 (11)	2 (11)
Pulmonary aspergillosis	2 (11)	1 (6)
Tachycardia	2 (11)	0 (0)
Anorexia	2 (11)	0 (0)
Nausea	2 (11)	0 (0)
Hypotension	2 (11)	0 (0)
Bone pain	2 (11)	0 (0)
Coagulopathy	2 (11)	0 (0)
Abdominal pain	2 (11)	1 (6)
Pharyngitis	2 (11)	0 (0)
Otitis	2 (11)	0 (0)
ICANS	1 (6)	0 (0)

Abbreviation: ICANS, immune effector cell associated neurotoxicity syndrome.

according to common terminology criteria, version 4.0. For the purpose of this analysis, CRS and ICANS were retrospectively graded according with the ASTCT 2019 consensus grading guidelines.[29] Efficacy was analyzed using the NCCN criteria,[30] including bone marrow aspirate and CSF analysis; MRD assessment by flow cytometry; and PET-CT and MRI scanning in patients with known EMD. In selected patients with measurable disease by PET-CT, metabolic tumor volume was calculated as previously described.[31] Secondary endpoints included objective and complete response rates (ORR/CRR), duration of response (DOR), progression-free survival (PFS), overall survival (OS) and duration of absolute B cell aplasia (BCA). The ORR/CRR was assessed at day +28, day +100, month +6, month +12 and month +18.

2.3 | ARI-0001 cell production and treatment

Patients were enrolled following screening and confirmation of eligibility and underwent a mononuclear cell collection using a Spectra Optia separator (Terumo BCT, Lakewood, CO). ARI-0001 cells were manufactured using the CliniMACS Prodigy system (Miltenyi).[32,33] Approximately 100×10^6 T-cells were cultured and stimulated with IL-7, IL-15, anti-CD3 and anti-CD28 antibodies. Cells were then transduced with a lentiviral vector containing the CAR gene construct. The construct comprises the single chain variable fragment of the anti-CD19 A3B1 monoclonal antibody attached to a transmembrane CD8 domain and 4-1BB/CD3z signaling domains (Figure 1). Following 6–9 days of expansion, the cell product was washed, cryopreserved,

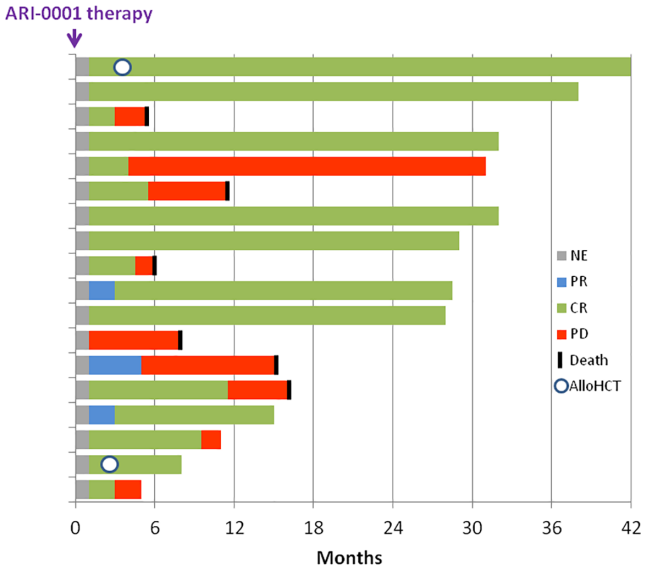

FIGURE 3 Swimmer plot for all patients with iEMD ($n = 18$). Green denotes complete remission, blue denotes partial remission, and red denotes refractory disease, progression, or relapse. Thick black lines denote "dead at last follow-up." Open circle represent the occurrence of allogeneic hematopoietic cell transplantation [Color figure can be viewed at wileyonlinelibrary.com]

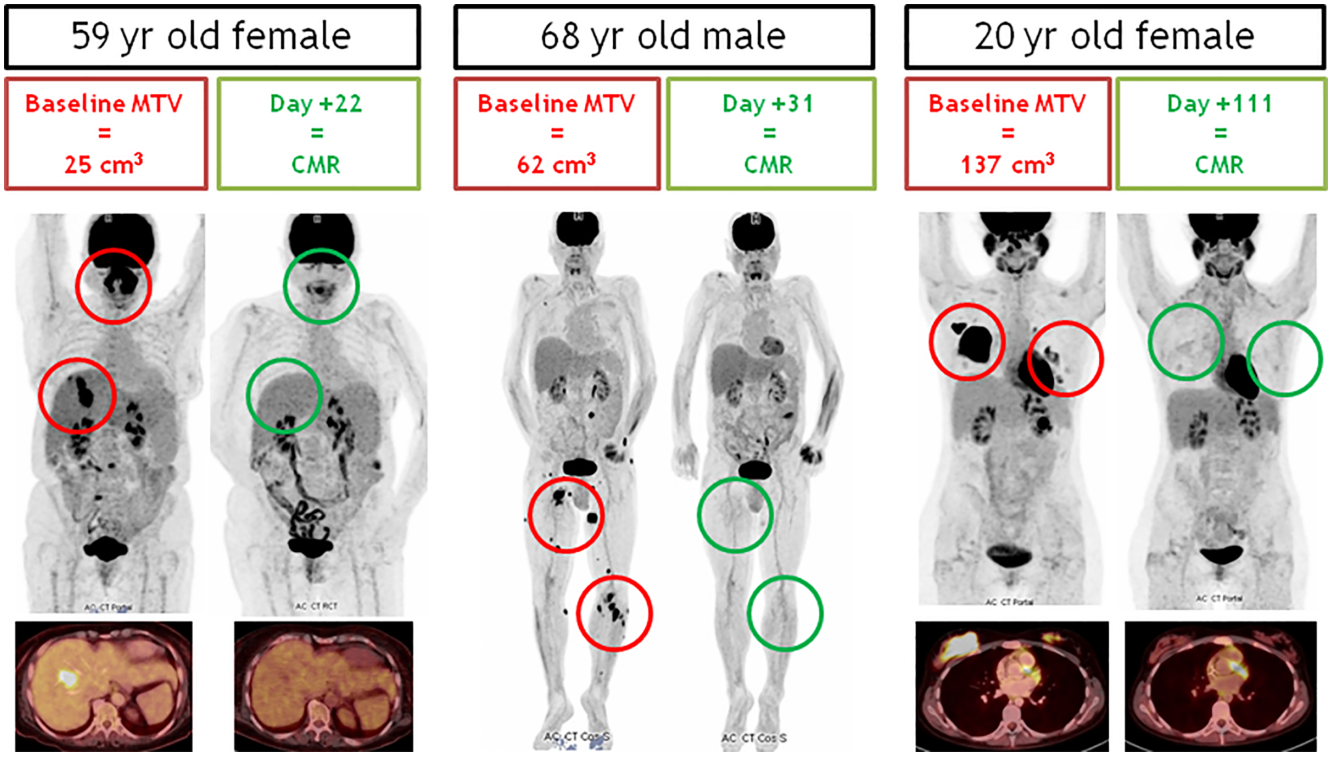

FIGURE 2 PET-CT scans of three different patients before and after ARI-0001 cell therapy. Post-therapy scans are those where the first complete metabolic response was documented, whenever that happened. Red circles highlight the most representative locations of abnormal [^{18}F] fluorodeoxyglucose uptake before therapy, while green circles highlight the same locations after therapy. MTV, metabolic tumor volume; CMR, complete metabolic response [Color figure can be viewed at wileyonlinelibrary.com]

and tested for identity, potency, sterility, and adventitious agents.[32]

Before ARI-0001 cell 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 1×10^6 ARI-0001 cells/kg. Even though the target dose changed during the CART19-BE-01 trial,[4] all patients with iEMD received a target dose of 1×10^6 ARI-0001 cells/kg. The first patient with iEMD received a single intravenous infusion of ARI-0001 cells on day 0, whereas the remaining 17 patients received the first fraction (10%) of ARI-0001 cells on day 0, followed by the second (30%) and third (60%) fraction separated at least by 24 h each only if there were no signs or symptoms of CRS. This amendment was motivated by three cases of lethal toxicity in the cohort of patients receiving a single intravenous infusion.[4]

2.4 | Statistical analysis

Response rates are presented with 95% exact Clopper-Pearson confidence intervals. PRM was calculated as a cumulative incidence considering disease relapse as a competing event. DOR, PFS, OS and duration of absolute BCA were plotted using the Kaplan–Meier method. Statistical analyses were performed using R (R Foundation for Statistical Computing, Vienna, Austria). The CART19-BE-01 trial (EUDRA no 2016-2972-29) is registered at clinicaltrials.gov (NCT03144583).

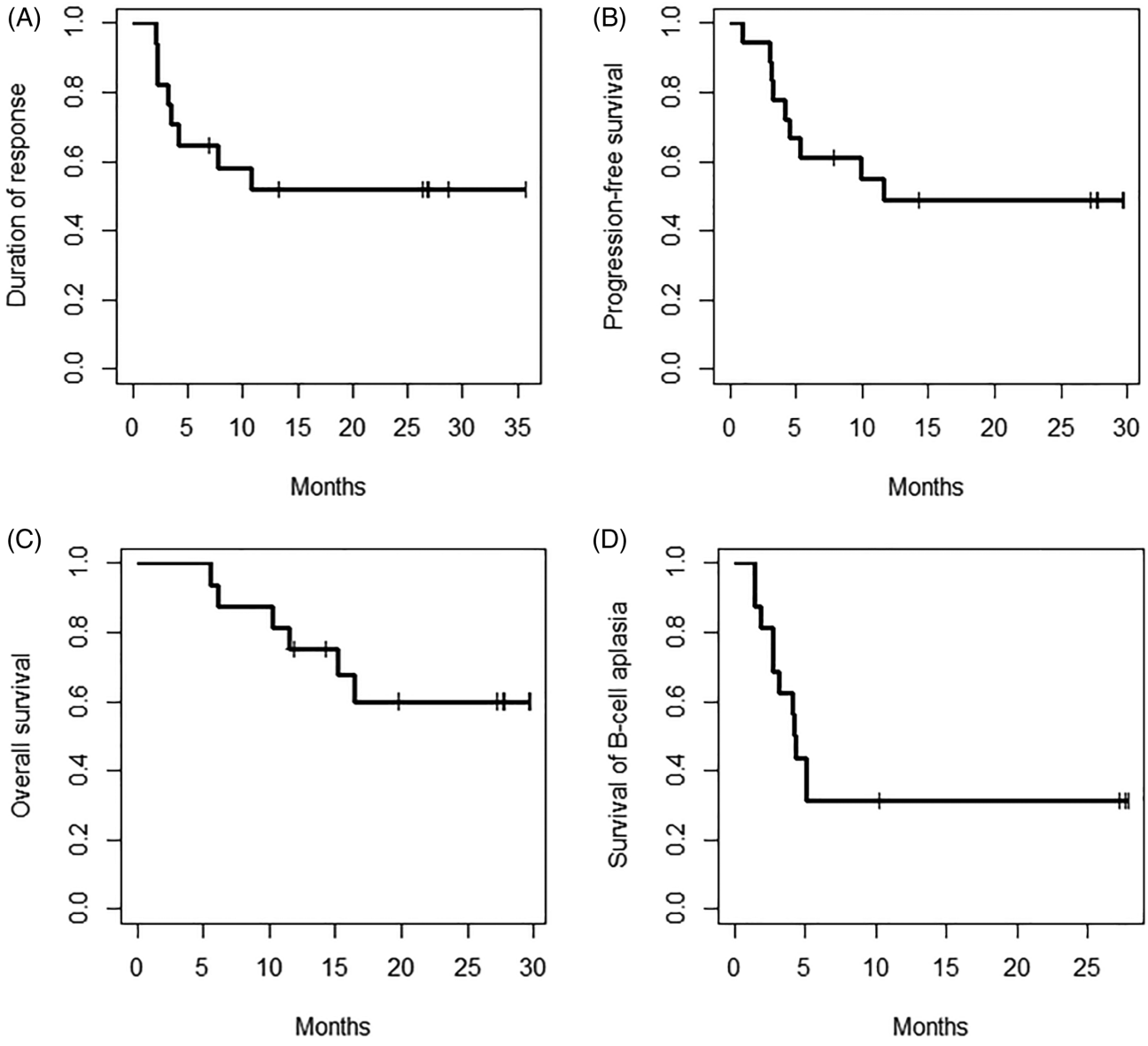

FIGURE 4 Clinical outcome of patients with acute lymphoblastic leukemia and iEMD in terms of (A) duration of response; (B) progression-free survival; (C) overall survival; and (D) survival of B-cell aplasia. Procedure-related mortality was not observed in the cohort and therefore not plotted

3 | RESULTS

3.1 | Baseline characteristics

A total of 59 patients (13 children, 46 adults) with R/R ALL were enrolled in the CART19-BE-01 study[4] and the consecutive CUP. Of this, 18 (30%) patients with iEMD were identified. Table 1 displays their baseline characteristics. Median age at infusion was 27 years (range, 8–68), including 5 (28%) pediatric patients. All were highly pretreated, including prior allo-HCT in 16 (89%) cases. Moreover, 15 (83%) patients required bridging chemotherapy while ARI-0001 cells were manufactured. Median bone marrow blast count at screening was 1% (range, 0–4) by morphologic assessment, with all patients having negative MRD by flow cytometry (0.01% sensitivity). Isolated EMD was detected by PET-CT in 78% (14/18) and CSF analysis in 28% (5/18). Patients received therapy a median of 50 days (range, 33–169) after study inclusion (i.e., signature of informed consent), and the median vein-to-vein time was 42.5 days (range, 26–166). In four patients, ARI-0001 cells were infused beyond 2 months of apheresis because of technical problems (e.g., bacterial contamination, defective viral transduction) leading to a second manufacturing procedure in three patients, and temporary interruption of the CART19-BE-01 trial in one patient.[4] The cutoff date was October 2021. At that time, the median follow-up for survivors was 26.7 months (range, 4.6–49.0) from ARI-0001 cell infusion and 28.6 months (range, 5.8–50.8) from study inclusion.

3.2 | Toxicity

CRS (any grade) occurred in 9/18 patients (50%, 95% confidence interval [CI]: 26%–74%), with a median onset time of 3 days (range, 0–6), and a median duration of 2 days (range 0–10) (Table 2). There were no cases of grade ≥3 CRS and 1 case (6%) of grade 1 ICANS. Tocilizumab was administered to one patient (6%) with grade 2 CRS. No patient received steroids for the treatment CRS or ICANS. Grade ≥3 neutropenia was observed in 15 patients (83%, 95% CI: 59%–96%), with a median duration of 8 days.[3–18] There was one case (6%, 95% CI: 14%–27%) of grade ≥3 anemia, and there were seven cases (39%, 95% CI: 20%–61%) of grade ≥3 thrombocytopenia. We did not observe any procedure-related deaths in this cohort. Hypogammaglobulinemia (any grade) was documented in 16 patients (89%, 95% CI: 65%–99%) at 1 month, including 10 patients (56%, 95% CI: 31%–79%) with an IgG concentration lower than 4 g/L.

3.3 | Efficacy

The best ORR at any time was 94% (95% CI: 73%–99%), with a CRR of 78% (95% CI: 52%–94%). All patients with CSF infiltration achieved a CR. In patients with PET-positive disease, complete metabolic responses were observed as soon as 3 weeks and as late as 4 months after infusion (Figure 2). Two thirds of patients with initial partial metabolic responses eventually achieved a complete metabolic response (Figure 3). Bone marrow and peripheral blood were also evaluated, even though there was no measurable disease at study inclusion. These assessments revealed a MRD-negative CRR of 94% (95% CI: 73%–99%) and 78% (95% CI: 52%–94%) at day +28 and +100, respectively. DOR, PFS and OS were 52% (95% CI: 32%–83%), 49% (95% CI: 30%–79%) and 61% (95% CI: 40%–92%) at 2 years (Figure 4). Median duration of absolute BCA was 4.3 months (2.8-NE). Two patients received an alloHCT at day +142 and +151 post ARI-0001 treatment. The cumulative incidence of relapse/progression was 51% at 2 years (95% CI: 26%–76%), all of which where CD19-positive. BCA loss preceded relapse/progression in 8/9 (89%) of patients from the series. All patients with relapsed/progressive

TABLE 3 Toxicity and efficacy of ARI-0001 cells in patients included in this study according to their age

	≤18 years $N = 5$	>18 years $N = 13$	≤25 years $N = 8$	>25 years $N = 10$
Toxicity				
CRS (any grade), % (95% CI)	80 (28–99)	38 (14–68)	63 (24–91)	40 (12–74)
CRS (grade ≥ 3), % (95% CI)	0 (0–52)	0 (0–25)	0 (0–37)	0 (0–31)
ICANS (any grade), % (95% CI)	20 (1–72)	0 (0–25)	13 (0–53)	0 (0–31)
ICANS (grade ≥ 3), % (95% CI)	0 (0–52)	0 (0–25)	0 (0–37)	0 (0–31)
Efficacy				
Absence of MRD at day +28, % (95% CI)	100 (48–100)	92 (64–99)	100 (63–100)	90 (56–99)
Absence of MRD at day +100, % (95% CI)	80 (28–99)	77 (46–95)	88 (47–99)	70 (35–93)
Duration of BCA at 2 years, % (95% CI)	67 (30–100)	23 (9–62)	33 (11–100)	30 (12–77)
DOR at 2 years, % (95% CI)	80 (18–52)	42 (21–81)	75 (50–100)	33 (13–84)
PFS at 2 years, % (95% CI)	80 (18–52)	39 (19–77)	75 (50–100)	30 (12–77)
OS at 2 years, % (95% CI)	100 (NE)	50 (27–89)	100 (NE)	36 (15–87)

Abbreviations: BCA, B-cell aplasia; CRS, cytokine release syndrome; DOR, duration of response; ICANS, immune effector cell-associated neurotoxicity syndrome; MRD, measurable residual disease (determined by flow cytometry in blood, marrow and cerebrospinal fluid); NE, not estimable; OS, overall survival; PFS, progression-free survival.

disease had EMD again, mostly in the original location, and five of them (56%) also had marrow disease upon relapse. Toxicity and efficacy results according to patients' age are displayed in Table 3.

4 | DISCUSSION

Thanks to the CART19-BE-01 trial, ARI-0001 cells are currently approved in Spain for the treatment of patients with R/R ALL older than 25 years of age under the Hospital Exemption Clause.[34] The drug was approved in February 2021 and the price/reimbursement was agreed with the Ministry of Health in June 2021. Our trial and the subsequent CUP have allowed for the inclusion of patients with iEMD, which had been excluded from many academic and commercially sponsored clinical trials. This is, therefore, one of the first series of patients with R/R ALL with iEMD treated with CART19-cells.

There are several aspects that characterize our population when compared with other similar reports[19–21]: (i) a high proportion (75%) of patients with prior exposure to blinatumomab and/or inotuzumab-ozogamicin; (ii) a high proportion (89%) of patients with who had already received an alloHCT; and (iii) the systematic evaluation by PET-CT and/or CSF analysis besides conventional blood and marrow analysis.

In our hands, the procedure was feasible, with 78% of patients receiving ARI-0001 cell therapy within 2 months from apheresis, and the entire cell production being accomplished with one procedure in 83% of patients. In terms of safety, we observed a 50% incidence of CRS with no cases of grade ≥3 CRS, which is comparable with similar studies.[19,21–23] In must be noted, however, that all patients from our iEMD cohort except one received ARI-0001 cells in a fractionated manner, which has been associated with a lower CRS rate compared to the original single-dose administration.[4] Besides fractionation, we also believe that the absence of bone marrow infiltration may play a role in the very low severe CRS rate, as observed by others.[1,2,5,6,35] Similar to our previous report, ARI-0001 therapy did not seem to cause any significant ICANS, not even in those patients with CNS disease. All in all, the safety of our product seemed in line, if not better, with what has been reported for other CART19 products in a similar clinical context.[19–22]

Efficacy was also comparable with other studies, with a 78% CRR including negative CSF and/or PET-CT, and a 2-year PFS rate of 49%. This PFS rate is particularly relevant because only two patients from this cohort underwent alloHCT while on CR and, therefore, the efficacy of our product is generally not confounded by subsequent therapy. Of note, EMD may take longer to respond to CART19-cells, as seen in some of our patients (Figures 2 and 3) and also, pseudoprogression may occur, complicating scan interpretation. Indeed, there is very little experience worldwide with the use of PET-CT in patients with ALL but, despite the difficulties, this technology has been very useful in our hands, and we believe it should be incorporated into the assessment of patients with ALL and EMD in the same way it is used for patients with lymphoma.

We measured the duration of absolute BCA in peripheral blood as a surrogate marker of ARI-0001 persistence and observed a median duration of 4.3 months in this patient population. Although this was equivalent to what we have seen in patients with ALL and marrow disease (data not shown) and other trials,[5,6,8,11] it is also true that most relapses we observed were CD19-positive and were preceded by BCA loss. Moreover, the pattern of BCA loss followed by CD19-positive relapse has been frequently observed in patients with low tumor burden.[36] We therefore believe that our efforts should focus on improving ARI-0001 cell persistence and, indeed, we are already testing a higher cell dose (3×10^6 cells/kg) in subsequent phase 2 trials intended for both adult and pediatric patients with ALL.

In conclusion, the administration of ARI-0001 therapy in patients with R/R CD19-positive ALL with iEMD achieved safety and efficacy outcomes that are comparable with similar products in patients with the more conventional marrow disease. We believe ARI-0001 cells constitute a potential therapeutic option in this situation of high unmet medical need. In February 2021, ARI-0001 cell therapy was approved, under the Hospital Exemption Clause, by the Spanish Medicines Agency (AEMPS) for patients with R/R ALL older than 25 years, including patients with iEMD. This is the first purely academic CAR-T product to ever receive approval in a European Union country.

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CONFLICT OF INTERESTS

Valentín Ortiz-Maldonado: consultant or advisory role (Kite Gilead, Celgene-BMS, Novartis, Janssen), travel grants (Kite Gilead, Celgene, Novartis, Roche, Takeda, Janssen), honoraria (Kite Gilead). Anna Alonso-Saladrigues: consultant or advisory role (Novartis), travel grants (Novartis), honoraria (Novartis). Anna Faura: consultant or advisory role (Novartis), travel grants (Novartis), honoraria (Novartis). Albert Català: consultant or advisory role (Novartis, Celgene), travel grants (Novartis, Celgene), honoraria (Novartis, Celgene). Eva Giné: consultant or advisory role (Kite Gilead, Janssen, Roche), research funding (Kite Gilead, Janssen, Roche). Marina Díaz-Beyá: consultant or advisory role (Celgene, Novartis, Jazz, Astellas). Alexandra Martínez-Roca: consultant or advisory role (Bristol Myers Squibb, Abbvie), travel grants (Kite Gilead, Abbvie, Janssen), speakers' bureau (Gilead, Abbvie); Luis Gerardo Rodríguez-Lobato: travel grants (Janssen, Amgen), honoraria (Janssen); Enric Garcia-Rey: honoraria (Novartis). Miquel Lozano: consultant or advisory role (Grifols), research funding (Terumo BCT, Sanofi-Genzyme, MacoPharma). María Rozman: consultant or advisory role (Novartis). Xavier Setoain: consultant or advisory role (General Electric, Takeda). Jordi Esteve: consultant or advisory role (Abbvie, Novartis, Celgene, Astellas, Jazz, Daiichi Dankyo, Roche, Amgen, Pfizer), travel grants (Celgene, Roche, Astellas, Daiichi Dankyo), research funding (Novartis, Celgene). Álvaro Urbano-Ispizua:

consultant or advisory role (Kite Gilead, Celgene, Miltenyi), travel grants (Kite Gilead, Celgene). Manel Juan: consultant or advisory role (Kite Gilead, Grifols), honoraria (Kite Gilead, Grifols). Sonia Rodríguez: consultant or advisory role (Novartis, Jazz, Shire/Servier, Amgen, Cellectis, Celgene/Bristol Myers Squibb), travel grants (Novartis, Jazz, Shire/Servier, Amgen, Celgene), honoraria (Novartis, Jazz, Celgene, Shire/Servier, Amgen). Marta Español-Rego, Nuria Martínez-Cibrián, Laura Magnano, Daniel Benítez-Ribas, Juan Gonzalo Correa, Joan Cid, Montserrat Rovira, Mercedes Montoro-Lorite, Raquel Cabezón, Enric Garcia-Rey, Georgina Pedrals, María Rozman, Susana Rives, Mariona Pascal and Julio Delgado have no competing interests to disclose.

AUTHOR CONTRIBUTIONS

Valentín Ortiz-Maldonado, Julio Delgado, and Susana Rives designed the clinical trial and wrote the paper; Jordi Esteve, Manel Juan, and Álvaro Urbano-Ispizua provided significant contribution to the study analysis; Valentín Ortiz-Maldonado, Nuria Martínez-Cibrián, Jordi Esteve, Luis Gerardo Rodríguez-Lobato, Eva Giné, Juan Gonzalo Correa, Marina Díaz-Beyá, Laura Magnano, Mercedes Montoro-Lorite, Montserrat Rovira, Alexandra Martínez-Roca and Julio Delgado looked after adult patients; Susana Rives, Anna Alonso-Saladrigues, Albert Català, Anna Faura, Nuria Conde and Georgina Pedrals looked after pediatric patients; Marta Español-Rego, Daniel Benítez-Ribas, Mariona Pascal, Raquel Cabezón and Manel Juan manufactured and monitored ARI-0001 cells; Xavier Setoain and Sonia Rodríguez evaluated PET-CT scans; María Rozman and Montserrat Torrebadell performed morphologic and immunophenotypic evaluation of CSF and blood or marrow samples; Joan Cid, Enric Garcia-Rey and Miquel Lozano performed leukocytaphereses; Julio Delgado performed the statistical analysis. All authors reviewed the study data, read, and approved the manuscript.

PATIENT CONSENT

All patients treated with ARI-0001 cells (CART19-BE-01 trial or compassionate use program) provided informed consent in writing.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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