Title

Pilot study with ARI0002h, an academic BCMA-directed CAR-T Cell therapy with fractionated initial infusion and booster dose for the treatment of patients with relapsed/refractory multiple myeloma

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Abstract

Background

CARTBCMA-HCB-01 aimed to assess safety and efficacy of ARI0002h, an academic, humanized BCMA CART in patients with relapsed/refractory (R/R) multiple myeloma (MM).

Methods

CARTBCMA-HCB-01 (NCT 04309981/EudraCT 2019-001472-11) is a pivotal, single-arm, multicentre and open label study in which ARI0002h was administered to patients with RR MM up to 75 years-old, two or more previous lines of therapy including a proteasome inhibitor, an immunomodulating agent and a CD38 monoclonal antibody, measurable disease and no previous BCMA-directed therapy. Patients received an initial fractionated infusion of $3x10^6$ CAR^+T-cells/kg in three aliquots and a non-fractionated booster dose of up to $3x10^6$ CAR^+T-cells/kg, at least 3 months after the first infusion. The primary endpoints were overall response rate (ORR) after first infusion and proportion of patients developing cytokine release syndrome (CRS) or neurotoxic events in the first 30 days in patients who received treatment. Here we present an interim analysis of the ongoing trial; enrolment has ended.

Findings

Between June 2nd, 2020, and February 24th, 2021, 30 patients received ARI0002h [median age 61 (IQR 53-65), female/male 40%/60%]. Results of the planned interim analysis (cut-off date October 20th, 2021), with a median follow-up of 12·1 months (IQR 9·1-13·5) revealed an ORR of 100% with 50% ≥ complete responses, 30% very good partial responses and 20% partial responses within the first 3 months. CRS was observed in 80% of patients (all grades 1-2). No cases of neurotoxic events were observed. Persistent grade 3-4 cytopenias were observed in 67% (n=20) of patients. Infections were reported in 67% of patients. Three patients had died: 1 due to progression, and 2 patients in response due to a head traumatism and an infection.

Interpretation

ARI0002h administered in a fractioned manner with a booster dose after 3 months can provide deep and sustained responses in patients with R/R MM, with a relatively low-grade toxicity, especially neurologic events, and the possibility of a point-of-care approach.

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Introduction

The survival of multiple myeloma (MM) patients has significantly improved in recent years after the incorporation of the combination of proteasome inhibitors (PI), immunomodulating agents (IMiDs) and anti-CD38 monoclonal antibodies (MoAb). Still, a large proportion of patients continue to relapse and multidrug resistance remains an important challenge leading to poor outcomes in patients with relapsed or refractory (RR) MM.[1,2]

Chimeric antigen receptor T (CART)-cell therapy has emerged as a promising option for RR MM. There are several products targeting B-cell maturation antigen (BCMA) under clinical investigation using different approaches in terms of origin of the antigen-recognition domain (murine, humanized, human, llama), co-stimulatory domain (4-1BB and CD28) and transduction method (lentiviral, retroviral, transposon).[3] Nevertheless, only two BCMA CART idecabtagene vicleucel (Ide-cel; Abecma, Bristol Myers Squibb) and ciltacabtagene autoleucel (Cilta-cel; CARVYKTI, Janssen Biotech, Inc.) have been approved by the Food and Drug Administration and the European Medicines Agency for the treatment of MM after at least four and three prior lines of therapy, respectively, including a PI, an IMID and an anti-CD38 MoAb.[4,5] The Ide-cel study reported an overall response rate (ORR) of 73% with 33% complete responses (CR) [26% of stringent CR (sCR)] with a median progression-free survival (PFS) of 8.8 months (95%CI 5·6-11·6) and some expected CART-related adverse events: cytokine-release syndrome (CRS) in 84% (grade≥3 5%), immune effector cell-associated neurotoxicity syndrome (ICANS) in 18% (grade≥3 3%) and cytopenias.[6] In a phase III clinical trial, Ide-cel showed improved responses and PFS compared to standard of care in triple-exposed patients.[7] The 2-year update of Cilta-cel showed an ORR of 97.9% with 82.5% of sCR in 97 MM patients treated with 0.75 x$10^6$$CAR^+$/kg. Median PFS and overall survival (OS) were not reached after a median follow-up of 27.7 months. CRS was reported in 95% (grade≥3 4%) and neurotoxicity in 21.6% (grade≥3 12.3%), including both ICANS and other neurotoxicities. Parkinsonism symptoms occurred in 6 patients, with one related-death and 2 deaths due to other causes. Parkinsonism-like neurotoxicity decreased to <0·5% after patient management strategies.[8] Recently, the first allogeneic BCMA-CART (ALLO-715) has reported an ORR of 71% including 25%≥CR, with a very short median time from enrolment to lymphodepletion (LD).[9]

Our institution has developed two academic CART constructs; one directed against CD19 (ARI-0001; Varnimcabtagene autoleucel) and another against BCMA (ARI0002h). The CART19-BE-01 multicentre clinical trial with ARI-0001 for adult and paediatric $CD19^+$ malignancies led to its approval as hospital exemption in Spain in February 2021, being to our knowledge the first academic CART in clinical use in Europe.[10-12] From our previous experience treating CD19 malignancies with ARI-0001, we observed how administering the initial dose in a fractionated manner might diminish severity of immune-related side effects without reducing efficacy, although this study was not specifically designed to compare outcomes of a fractionated vs. non-fractionated infusion.[11,13]

ARI0002h is a humanized 4-1BB-based BCMA-CART, lentivirally transduced on autologous T-cells obtained by peripheral blood leukapheresis that has proven efficacy in preclinical *in vitro* and *in vivo* approaches.[14] These findings led to the development of a pivotal study to assess the safety

and efficacy of ARI0002h. Three strategies were adopted to improve outcomes. Firstly, the murine single chain variable fragment (scFv), obtained from the J22.9 antibody, was humanized to reduce immunogenicity. Preclinical experiments were conducted to prove non-inferiority between constructs containing the humanized versus murine scFv. Second, the first dose was fractioned into 3 aliquots to reduce toxicity. Finally, a second infusion of ARI0002h was planned months after the first infusion, as an experimental attempt to improve persistence and response.

Methods

Study design and participants

CARTBCMA-HCB-01 is a pivotal, single-arm, open label study conducted in 5 centres in Spain. The aim of the study was to evaluate the safety and efficacy of ARI0002h in patients with RRMM after an initial fractionated infusion and a non-fractionated booster dose, administered at least 3 months after the first infusion in patients presenting some degree of response and no limiting side effects. Main eligibility criteria were age between 18 and 75 years old, Eastern Cooperative Oncology Group performance status 0-2, two or more previous lines of therapy including a PI, an IMID and an anti-CD38 antibody, refractoriness to the last line and measurable disease (serum and urine monoclonal protein >10g/L or 200 mg/24h, involved FLC >100mg/L) according to the International Myeloma Working Group (IMWG) criteria[15] and a life expectancy of more than 3 months. Exclusion criteria included previous BCMA-directed therapy and a non-adequate organ system function including an estimated glomerular filtration rate <50 ml/min. Study protocol and participating sites are summarized in the Appendix p2. Patients provided written informed consent. The study protocol was approved by the Ethics Committee of Hospital Clínic de Barcelona (HCB) and was conducted in accordance with the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects.

Procedures

Clinical coordination and vector viral production were conducted in HCB. Two centres were responsible for CART production: HCB and Clínica Universidad de Navarra (CUN) (Appendix p6). These and three additional centres treated patients. Subject features including sex were defined by electronic medical records. Race or ethnicity were not collected. Patients were evaluated for inclusion and proceeded to leukapheresis in their respective centres. Fresh apheresis products were sent to one of the two production centres. The target dose was $3x10^6CAR^+$cells/kg for the first infusion and a second dose of up to $3x10^6CAR^+$cells/kg was also obtained, when possible. The final product was cryopreserved. Bridging therapy (BT) was allowed in the period between apheresis and LD according to investigator's choice. LD was administered intravenously on days -6 to -4 (prior to infusion) and included fludarabine (30 mg/m^2 per day; total dose 90 mg/m^2) and cyclophosphamide (300 mg/m^2 per day; total dose 900 mg/m^2). The first infusion was split into three administrations of 0·3 (10%), 0·9 (30%) and $1{\cdot}8x10^6CAR^+$cells/kg (60%) intravenously

on days 0, +3 and +7, with at least 24h between doses in all cases. If adverse events occurred between administrations, remaining doses were adjusted until resolution.

The booster dose of up to $3x10^6CAR^+$cells/kg was administered in a single intravenous infusion after day 100 in patients with some degree of response and no limiting side effects after the first dose including grades 3-4 CRS or ICANS and other adverse events of interest (persistent cytopenias, macrophage activation syndrome (MAS)). LD was readministered with the same scheme only in patients without CART persistence in peripheral blood (PB).

Patients were followed for 36 months, or until progression or death. Subjects could be removed from the study based on patients' decision. Laboratory monitoring was planned in the following days/months from infusion: day 1, 10, 14, 21, 28, 35, 42, 56, 70, 84, 100, months 4, 6, 7, 8, 9, 10, 11 12, 15, 18, 21,24, 27, 30, 33 and 36. Bone marrow aspirates assessing MRD by next generation flow cytometry at a sensitivity of $1x10^{-6}$ were planned on day 28, 100, month 6, 12, 18 and 24. Evaluation was performed using the 2-tub 8-color according to the EuroFlow platform, using a FACSCanto™ (BD Biosciences, La Jolla, CA, United States) flow cytometer and Infinicyt 2.0 software (Cytognos SL, Salamanca, Spain). Any detectable level of MRD $>1x10^{-6}$ was considered positive. PET-CT were planned at screening and on day 100 and month 12 to evaluate plasmacytomas. MM assessment was planned in the following days/months from infusion: day 28, 56, 100, months 4 to 12, month 15, 18, 21,24, 27, 30, 33 and 36. Responses were assessed according to IMWG criteria (Appendix p6).[16] Adverse event monitoring was performed in all follow-up visits mentioned previously, including a daily monitoring from infusion day until discharge from the hospital. CRS and ICANS were assessed according to the American Society for Transplantation and Cellular Therapy consensus.[17] Intravenous immunoglobulins could be administered according to local guidelines when IgG levels were below 400 mg/dl.

Samples were obtained from PB and bone marrow (BM) for correlative studies (Appendix p10). BCMA expression on BM plasma cells was measured by flow cytometry (PE anti-human CD269 (BCMA) Antibody; Cat #: 357504, Biolegend) at baseline and in MRD positive disease. Molecules of BCMA were quantified using the BD QuantiBRITE™ Beads (molecules/cell). The peak and persistence of ARI0002h by polymerase chain reaction (PCR), soluble BCMA (sBCMA) and presence of human anti-human antibodies (HAHA) were measured in PB samples. Kinetics of ARI0002h in the peripheral blood was measured by quantitative polymerase chain reaction (qPCR) determining the time course of vector transgene WPRE to elucidate the amount of ARI0002h copies per cell. Inmunogenicity against ARI0002h was evaluated by flow cytometry on Attune Next (Invitrogen, Thermofisher Scientific) flow cytometer to determine the presence of human anti-human antibodies (HAHAs). For further information, refer to the Appendix p7. None of the procedures or analysis have been done differently from their description in the protocol. After evaluation of initial results, a second cohort of 30 additional patients has been approved for recruitment.

Outcomes

The proportion of patients who developed a CRS and/or ICANS in the first 30 days after ARI0002h administration was assessed as the primary safety endpoint. The primary efficacy endpoint was

ORR in the first 100 days of infusion, defined as achievement of at least partial response (PR).[15] Secondary endpoints included the following: CR rates at 100 days and six months from infusion, response at six and twelve months, time to best response and time to CR, measurable residual disease (MRD) negativity rates at day 100 and month six, plasmacytoma evaluation by positron emission tomography-computed tomography (PET-CT) at day 100, duration of response (DOR), PFS, PFS at 12 months and OS, presence of infusion reactions, tumour lysis syndrome, neurotoxicity besides ICANS, prolonged cytopenias defined as the reduction of neutrophil or platelet peripheral blood counts, grade 3 or 4 after 4 weeks from infusion and some correlative studies such as ARI0002h persistence, BCMA expression and sBCMA. Quality of life evaluation was also prespecified in the protocol of the study but results are not provided since data are not available. DOR was defined as the time between first response and disease progression. PFS was defined as the time between infusion of ARI0002h and disease progression or death. OS was defined as the time between infusion of ARI0002h and death due to any cause. Therefore, origin time was infusion of ARI0002h cells, start time was same as origin time for PFS and OS and time of disease response evaluation for DOR, and end times were progression for DOR, progression or death for PFS and death for OS. Reasons for censoring were the following: last follow-up without progression or death without progression for DOR, last follow-up without progression or death for PFS and last follow-up without death for OS.

Statistical analysis

It was initially proposed to recruit patients with the objective to treat 30 subjects. It was assumed that a percentage of patients would not achieve the objective of being treated with ARI0002h due to early progressions after or even before the performance of the apheresis. A 20% of pre-treatment patient loss was estimated so it was defined that 36 patients would be necessary to achieve the 30 administrations expected. Sample size calculation was limited for funding reasons. Estimations made were based in population of efficacy analysis (defined as patients who received at least a fraction of ARI0002h; n=30). Two plausible scenarios were reflected: (1) ORR in the first 100 days ≥ 80%. It would allow to rule out with 95% confidence that the real ORR is below 65% in a population similar to the one studied. (2) ORR in the first 100 days ≥ 70%. It would allow to rule out with 95% confidence that the real ORR is below 54% in a population similar to the one studied.

Statistical Analysis Plan (SAP) established that the main population for the safety set would be patients who received at least one cycle of LD and the main population for efficacy analyses was the population of patients who received treatment with ARI0002h (n=30 for both sets). Statistical analyses were performed with SAS System (release 9.4) and R (R Foundation for Statistical Computing, Vienna, Austria). A p-value <0.05 was considered statistically significant. Due to the open-label non-randomised nature of the study, the statistical analysis was descriptive. However, for illustrative reasons, some p-values from posthoc comparisons are provided, which should be considered informative but not conclusive: vein-to-vein time according to receiving or not BT, response and survival according to receiving or not the full first dose, expansion after booster dose according to receiving or not LD, survival according to the

achievement of CR, survival according to the presence of plasmacytomas and correlation of BCMA with response. P-values of categorical variables were calculated with Chi-squared or Fisher's exact test according to sample size. P-values of continuous variables were calculated with the Student's t-test, Wilcoxon-Mann-Whitney or Wilcoxon signed-rank test according to their adherence to the Gaussian distribution tested with Saphiro-Wilk test. If appropriate, p-values were adjusted for multiple comparisons with the Benjamini-Hochberg method. DOR, PFS and OS were plotted using the Kaplan-Meier method. Survival calculations between independent groups were tested with the Log-rank test. When appropriate, 95% confidence intervals (95%CI) calculated using the Wilson score method are provided for endpoint measurements. For survival times, CI were calculated with the "log" method. This study is registered with ClinicalTrials.gov NCT 04309981 and EudraCT 2019-001472-11.

Role of the funding source

None of the study funding agencies have participated in the study design, collection, analysis, interpretation of data, writing of the report or in the decision to submit the paper for publication.

Results

Between June 2nd, 2020, and February 24th, 2021, thirty-five patients were enrolled, but only 33 patients underwent leukapheresis due to two MM progressions. In the end, 30 patients (85·7%) received ARI0002h due to two additional MM progressions and an infectious death before final product release. There were no discontinuations due to manufacturing failures (Figure 1). Analyses were performed on the population of patients who received treatment with ARI0002h (n=30). Patients' baseline features are summarised in Table 1. Median age was 61 years (IQR 53-65); 14 of 30 (47%) patients presented plasmacytomas at inclusion with 6 of 30 (20%) presenting a true extramedullary (EMD), non-paraskeletal (PS) location. Up to 10 of 30 (33%) of patients had high-risk cytogenetics, including 7 of 30 (23%) with *TP53* alterations. Median previous treatment lines were 4 (3-5), with 20 of 30 (67%) triple-class refractory and 7 of 30 (23%) penta-class refractory. Fourteen out of 30 (47%) patients received BT. Assessment of disease before and after BT showed no change or even progression of the serum M-protein and/or free light chain (FLC) involved in 13 of 30 (43%) (Appendix p11). Twenty-eight of 30 (93%) patients had previously received an autologous stem cell transplantation (SCT), including 4 of 30 (13%) that also received an allogeneic SCT.

All patients were scheduled to receive a first infusion of $3x10^6CAR^+$cells/kg (total dose), split into three fractions, but five patients did not receive the third fraction due to adverse events (*see Safety*). The second administration of ARI0002h in a single infusion of 100% of the dose was given to 24 of 28 (86%) eligible patients. The remaining two patients were not eligible due to one extramedullary progression and one death (cranial traumatism), in day 100 and month 4, respectively. Four of the 28 (14%) patients did not receive the booster dose due to prolonged

cytopenias, diagnosis of a secondary neoplasm, macrophage activation syndrome and lymphocytosis due to CART expansion (Appendix p12). Median time to booster dose was 4 months (IQR 3-5; range 3-7). Nine of 24 patients (38%) received a second LD regimen prior to the booster dose, based on CART persistence in PB.

Here, we first present safety and efficacy results of the planned interim analysis (PIA) with a cut-off date of October 20th, 2021 [median follow-up 12·1 months (IQR 9·1-13·5)] to initiate regulatory review by the Spanish National Competent Authority (SNCA) and thus receive authorization for hospital exemption. Interim efficacy and safety information is provided to the SNCA for the rolling review on a periodic basis, including information regarding safety and efficacy after the administration of the booster dose. At the cut-off date of the PIA, general follow-up and follow-up after the booster dose was limited. In order to provide scientifically relevant data after longer follow-up of patients, a post-hoc analysis was performed with a cut-off date of May 15th, 2022 [median follow-up 18 months (IQR 15·2-19·6)].

The median manufacturing time was 10 days (IQR 9-10) with a mean transduction rate of 56% (SD 25·3). All final products for the first infusion were successfully obtained at the first attempt except one, which was produced with a second apheresis. In 19 of the 24 patients that were reinfused, $3x10^6CAR^+$cells/kg were available for the booster dose, $1·8x10^6CAR^+$cells/kg in three patients and $1·2x10^6CAR^+$cells/kg in two (Appendix p12). Median turnaround time, defined as days (d) from apheresis reception to product liberation, was 30 (IQR 26-36; range 19-45). In patients requiring urgent treatment, their products were released as fast as in 19 days. Median vein-to-vein time was 43d (IQR 35-54), with differences among patients who did or did not receive BT: 54d (IQR 44-58) vs. 35·5d (IQR 30-43) (p=0·001).

At the time of data cut-off (October 20th 2021), 10 of 30 (33%; 95%CI 19.2-51.2) patients had discontinued: 8 patients developed disease progression and 2 died without progression (1 after a cranial traumatism and 1 after severe SARS-CoV-2 pneumonia). These two deaths occurred in months 4 and 9, respectively. An additional death occurred in a patient with disease progression. No deaths occurred within the first month of treatment.

CRS was observed in 24 of 30 (80%) patients, always after receiving at least the second fraction of 30% (total dose 40%), with no grades 3 or higher [15 of 24 (62·5%) grade 1, 9 of 24 (37·5%) grade 2]. Median time to onset of CRS was 7d (IQR 4.5-8) from the first fraction (10%), with a median duration of symptoms of 2d (IQR 0-14). Tocilizumab was administered in 19 of 30 (63%) of patients, mainly for persistent grade 1 CRS, and 10% of patients received steroids. Due to CRS, a clinical decision was made that 5 patients would not receive the third fraction of $1·8x10^6CAR^+$cells/kg. There were no differences in response rates [CR in complete dose vs. incomplete 68% (n=17 of 25) vs. 60% (n=3 of 5); p=0·73] or PFS between these five patients who received only the first two fractions compared to those receiving the full dose [median PFS complete dose vs. incomplete 14·5 months (95%CI 12·8-not reached) vs. not reached (95%CI 12·1-not reached); p=0·83]. No cases of ICANS or late neurologic events were observed. None of the patients who received the booster dose presented CRS, ICANS or any adverse events of interest.

One mild infusion reaction and one moderate tumour lysis syndrome were reported. Prolonged cytopenias were reported in 20 of 30 (67%) of patients (Table 2). Median duration of grade 4 neutropenia was 35 days (95% CI 26-44) and time to complete resolution of cytopenias was: neutropenia 4 months (95% CI 3-5), thrombocytopenia 11.7 months (95% CI 5.5-17.9) and anemia 3.1 months (95% CI 1-13.2). All patients recovered without requiring a stem cell boost. The overall safety profile is depicted in Table 3.

Infections were reported in 20 of 30 (67%) patients. Forty-five infectious episodes [7 of 45 (16%) grade≥3] were reported with most patients experiencing an average of 1-2 infection episodes (Appendix p13). Respiratory tract infections were the most common corresponding to 53% (24 of 45) of episodes, including 10% of SARS-CoV2 infections. Other relevant adverse events were a new diagnosis of colon adenocarcinoma, considered non-related to ARI0002h, and one reactivation of hepatitis B virus. Three cases of MAS occurred, two of them in combination with a grade 1 CRS. All cases resolved completely.

ORR during the first 100 days from infusion was 100% (30 of 30), including 80% (24 of 30) of very good partial response (VGPR) or better [50% of CR (15 of 30), 30% VGPR (9 of 30) and 20% (6 of 30) PR]. Time to CR was 3·8 months (IQR 1-11·6). On day 28, MRD by NGF was evaluable in 73% (22 of 30) of samples, with all patients but one (95%; 95%CI 78·2-99·2) presenting a negative result. On day 100, 24 of 26 (92%; 95%CI 75·8-97·9) evaluable samples were negative (Appendix p14).

Regarding the booster dose, 14 of 24 patients (58%; 95%CI 38·8-75·5) already had a sCR prior to reinfusion, 6 of 24 patients (25%; 95%CI 11·9-44·9) maintained the response (all VGPR) and 4 of 24 patients (17%; 95%CI 6·7-35·8) improved the response after booster dose, 2 patients from VGPR and 2 from PR, all to CR (Figure 2C).

On May 15th 2022, after a median follow-up of 18 months (IQR 15·2-19·6), ORR was 100% (30 of 30) (95%CI 88·6-100) with 67% CR (20 of 30) (95%CI 48·8-80·8), 27% VGPR (8 of 30) (95%CI 14·2-44·4) and 7% PR (2 of 30) (95%CI 1·8-21·3). Eighteen of the 20 (60%) patients in CR had a sCR. Responses at month 6 were 47% CR (14 of 30) (95%CI 30·2-63·8%), 37% VGPR (11 of 30) (95%CI 21·9-54·5), 7% PR (2 of 30) (95%CI 1·8-21·3), 7% progressive disease (2 of 30) (95%CI 1·8-21·3) and 3% death without relapse (1 of 30) (95%CI 0·6-16·7). Responses at different time points are shown in the Appendix p15. Median time to best response was 3·3 months (95%CI 1-3·4), with some patients improving responses after month 3. The differences in ORR in the first 100 days and at this follow-up accounts for the fact that responses deepen over time, with 5 of 20 (25%) patients achieving a CR after month 3, and 5 of 30 (17%) patients achieving their best response after 6 months (1 up to VGPR and 4 to CR) (Figure 2A-B). In terms of MRD, at months 6 and 12, 20 of 25 (80%) and 16 of 20 (80%) evaluable patients remained MRD negative (Appendix p14).

On May 15th 2022, median DOR and OS were not reached (DOR 95%CI 12·9-not reached; OS 95%CI 8·0-not reached), and median PFS was 14·5 months (95%CI 12·8-not reached) (Figure 3A-B). Fourteen patients had presented a PFS event: 12 developed disease progression and 2 died without progression as previously described. The PFS rate at 12 months was therefore 70% (95%CI 55·4-88·5). Median DOR in patients who achieved a CR vs. less than CR was not reached

(95%CI not reached-not reached) vs. 9·7 months (95%CI 6·0-not reached; p=0.004) (Appendix p 17). The OS rate at 12 months was 86·5% (95%CI 75·1-99·7).

Fourteen of 30 (47%) patients had plasmacytomas in the PET-CT performed at inclusion: 8 of 30 (27%) PS and 6 of 30 (20%) EMD. A PET-CT scan was planned at day 100, showing a metabolic response in 13 of 14 (93%; 95%CI 68·5-98·7) patients. No differences in terms of PFS or OS were detected according to the presence or absence of plasmacytomas at inclusion (Appendix p18). Of note, the 6 patients with plasmacytomas that presented disease progression died, while all progressed patients without plasmacytomas remain alive.

ARI0002h detection in PB by PCR showed a median persistence of 5·0 months (95%CI 3·8-6·2). On day 100, month 6 and month 12, 52% (15 of 29), 28% (7 of 25) and 20% (4 of 20) of patients had detectable CART in PB, respectively (Appendix p19). The peak of expansion was observed on day 14 for most patients (range 7 days-6 months) (Appendix p20). Mean copies/genome at the peak of expansion were 11·1 (SD 14·2). Of 9 patients with an available sample at relapse, 3 (33%) still had detectable CART in PB.

After the booster dose, 12 of 24 patients (50%) presented a low-grade expansion immediately after administration, with a mean peak of 4 copies/genome (SD 9·2) (Appendix p20). No correlation was found between prior LD administration and expansion [3 of 8 (38%) patients receiving LD expanded vs 9 of 16 (56%) without LD expanded; p=0·67].

Mean BCMA molecules/cell on malignant BM plasma cells by flow cytometry at inclusion was 1306·5 (SD 889). The median change in BCMA molecules/cell in the 6 paired samples available at relapse showed a decrease from 1784 to 1001 molecules/cell (p=0.054). None of the cases had a complete loss of BCMA expression. Soluble BCMA was detectable in PB of all patients at inclusion with a mean of 89·3 ng/mL (SD 124·6). A significant decrease was observed in all patients on days 28 and 100 (p<0·0025 at both timepoints), and the 12 patients who relapsed had detectable sBCMA at the end-of-treatment sample, with non-significant differences compared to the sBCMA values at inclusion (Appendix p21).

Positivity of HAHAs was not sustained in time for each individual patient. We detected HAHAs in 21 of 30 (70%) patients , with positive HAHAs on days 28, 100, months 6 and 12 in 6·9% (2 of 29), 3·7% (1 of 27), 12% (3 of 25) and 37·5% (6 of 16), respectively (Appendix p22). At relapse, 8 of 12 patients had available HAHA measurements, of which only two were positive (25%).

Discussion

CAR T-cell therapy is standing out as a promising option for patients with heavily treated RRMM. Here, we show that ARI0002h, an academic CART administered in a fractioned manner and with the possibility of adding a booster dose after day 100, can provide deep and sustained responses with low-grade toxicity in this subset of patients with a presumably poor prognosis. In this study, all treated patients presented at least a partial response, with outstanding results in terms of MRD negativity by NGF as early as in the first evaluation performed on day 28. The development of CRS with ARI0002h was similar to other BCMA-CART therapies, showing a lower grade of

severity, with no grades 3 or above and no cases of ICANS or late neurotoxicity occurred. Therefore, ARI0002h might be a reasonable alternative to other BCMA CART constructs[3], including the already approved Ide-cel and Cilta-cel. Still, this study has methodological limitations in terms of design and analysis, including the small sample size, leading to wide 95% CIs.

We attribute the lower incidence of immune-related side effects, especially severe cases, to the fractionation of the first dose, as previously observed with ARI0001 in CD19 malignancies.[11] Still, other factors such as construct features, manufacturing process and total cell dose administered might play an important role in safety. Patients who received only two fractions of the first dose showed similar efficacy compared to those receiving the full dose. These patients develop an early CRS probably reflecting a faster in vivo expansion of the CART which may explain the similar outcome. Prolonged cytopenias and infections were a common adverse event, with a similar profile to that reported in other BCMA-CART studies.[6,8] Cilta-cel reported 58% of infections[8] and a retrospective analysis showed 47 infection events in 29 (53%) patients after a BCMA CART.[18]

Some patients with MM may present soft-tissue involvement in the form of PS or EMD plasmacytomas. The treatment of these patients remains a highly unmet need since available treatments have poor efficacy.[19] The ORR and PFS of patients treated with ARI0002h according to soft-tissue involvement at inclusion did not differ significantly, highlighting the positive impact that may have this CART in this subgroup of MM.[6,20]

The incorporation of a second infusion of ARI0002h after day 100 of the first administration was to deepen and lengthen responses. No relevant side effects were observed and patients were rapidly discharged, therefore an outpatient or at-home management could be evaluated.[21,22] In terms of efficacy, four of 10 patients with measurable disease had an improved response. Since there is no comparison group, we cannot affirm that these results are only attributable to the second infusion. In other BCMA-CART trials, a deepening of responses over time has been reported. However, median time to best response reported in the Cilta-cel study was 2·6 months,[8] suggesting that most patients achieve the deepest response within the first three months. Although the booster dose may play a role in improving and lengthening responses, it is difficult to establish in this non-randomized trial, in which 14 out of 24 patients were already in CR prior to booster dose. The feasibility in terms of manufacturing, the potential benefits in response depth and the absence of related side effects warrants further investigation of the booster dose. An earlier administration with a randomization for the second dose could be helpful to clarify the efficacy of this approach.

ARI0002h is an academic CART that has been manufactured in two facilities in Spain, being a real "point-of-care" manufacturing approach in these two centres (Barcelona and Pamplona; 15 of 30 patients). This can increase the number of slots available for production, allowing a fast release when the clinical situation of the patient requires it, as short as 19 days. The high costs, manufacturing delays, and potential bottlenecks of centralised, industry-driven CART production may limit access to this therapy.[23-25] This coexists with an exponential increase in demand that will probably continue growing due to the presumable introduction to earlier lines of treatment.[26] In addition, despite the European Commission authorization for Ide-cel and Cilta-

cel, the products are not available in Spain and several other European countries because there is no reimbursement agreement. ARI0002h can be manufactured at up to one fourth of the cost of commercial CARTs. For these reasons, we believe that academic CARTs will become essential to improve access around the world.

Despite promising results, patients continue to relapse after ARI0002h, so strategies to overcome relapses are of pertinent interest. Correlative studies performed on patient samples highlight different mechanisms that may be responsible for ARI0002h relapses. A median persistence in PB of 5 months, although quite similar to other available BCMA-CARTs, is still short (Ide-cel reported persistence in 59% and 36% in months 6 and 12 and most Cilta-cel patients had transgene concentrations below the threshold of quantification at 6 months).[6,8] The short duration of CART persistence in PB contrasts with long response durations in terms of PFS. BCMA quantification on malignant plasma cells tends to decrease from baseline levels in most patients, but none of them become BCMA negative (sBCMA was positive in all patients at relapse). Finally, several patients had detectable CART at relapse, suggesting that CART exhaustion with increase of some surface markers[27] could play a role in shortening duration of responses.

Figure legends

Figure 1. CONSORT diagram.

Figure 2. (A) Overall response rate and response evaluation at consecutive time points. **(B)** Swimmer plot with the response of each individual patient (n=30). **(C)** Swimmer plot with the response of each patient after booster dose (n=24).

Figure 3. (A) Duration of response (DOR) **(B)** Progression-free survival (PFS) and overall survival (OS) of patients treated with ARI0002h after a median of 18 months of follow-up.

Data Sharing

Individual, de-identified participant data and data dictionary can be made available, with publication, at the request of qualified investigators whose proposed use of the data has been approved by IDIBAPS, after a data access agreement is signed. Requests can be made to the corresponding author (cfernan1@clinic.cat). Additional related documents are available at: https://clinicaltrials.gov/ct2/show/NCT04309981.

Declaration of interests

AO-C declares support for attending meetings from Janssen. **VG-C** declares receiving honoraria from Janssen, Pfizer, BMS/Celgene, GSK; support for attending meetings or travel from Janssen and GSK; participation on data safety monitoring or advisory board from Janssen. **VC** declares receiving honoraria from Janssen, BMS, Sanofi, GSK and Amgen; support for attending meetings or travel from Janssen; participation on data safety monitoring or advisory board from Janssen, Sanofi and Amgen. **PR-O** declares receiving honoraria from consulting activities from BMS, Janssen, Sanofi, Abbvie, Pfizer, Roche and GSK; honoraria from lectures from BMS, Janssen, Sanofi and GSK; support for attending meetings or travel from Abbvie; participation on data safety monitoring or advisory board from Janssen. **JLR** declares receiving consulting fees from Janssen; honoraria from Janssen, Amgen, Sanofi, Kite/Gilead, Novartis and BMS; support for attending meetings or travel from Kite/Gilead; participation on data safety monitoring or advisory board from Janssen, BMS and Novartis. **LL-C** declares receiving honoraria from Kite-Gilead, Celgene, Janssen and Novartis; support for attending meetings or travel from Kite-Gilead, Celgene, Janssen and Novartis; participation on data safety monitoring or advisory board from Janssen. **BM-A** declares invertorship in the patent of ARI0002. **LR** declares honoraria from Janssen, BMS/Celgene, Amgen, Takeda, Sanofi and GSK; participation on data safety monitoring or advisory board of Janssen, BMS-Celgene, Amgen, Takeda, Sanofi and GSK. **ML-P** declares receiving consulting fees from Celgene/ BMS; honoraria from Janssen and Kite Gilead; participation on data safety monitoring or advisory board from Celgene/BMS and Novartis. **LGR-L** declares honoraria from Janssen, GSK, Sanofi and BMS; travel grants from Janssen, Amgen, GSK, Pfizer and Sanofi; participation on data safety monitoring or advisory board from GSK and Sanofi. **AS-S** declares receiving travel grants from Jazz Pharmaceuticals, Pfizer and MSD. **JAP-S** declares research and travel support Takeda, Abbvie, Gilead, AMGEN, Jazz, Alexion, Pierre Fabre and Beigene; Educational activities/speaker/advisory with Gilead, Jazz, Alexion, AMGEN, Novartis, Janssen, BMS and MSD; participation on data safety monitoring or advisory board from Gilead, Jazz, Alexion, AMGEN, Novartis, Janssen, BMS and MSD. **BP** reports research funding from BMS, GSK, Roche, Beigene and Sanofi; consultancy fees from BMS, GSK, Janssen, Sanofi and Takeda; honoraria from Adaptive, Amgen, Becton Dickinson, BMS/Celgene, GSK, Janssen, Sanofi, and Roche; support for attending meetings from GSK. **FP** declares receiving grants from the Spanish Ministry of Health (ISCIII) and the Government of Navarra; honoraria from Janssen, Oryzon, Dialectica, Novartis, Instituto Roche, Servier, ViviaBiotech and Techspert; support for attending meetings or travel from Gilead, Celgene and Janssen; leadership or fiduciary role in RICORS Terav and IDISNA. **MJ** declares receiving research and/or travel support by Fundació

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Authors' contributions

AOC, BMA, LR, NT, RJ, SV, JSP, JD, MJ, MP, AUI and CFL participated in conception and design of the work. AOC and MER participated in the writing of the manuscript draft. AOC, VGC, VC, PRO, JLR, LLC, AZ, BP, SI, ALDC, MLP, ASS, JAPS, FP, JMM and MVM provided data and figures. AOC, VGC, VC, PRO, JLR, LLC, AZ, BP, SI, ALDC, MLP and CFL collaborated with data collection. AOC, MER, AZ, BP, SI, ALDC, LGRL, SV and JSP performed data analysis and interpretation. All authors revised the article and gave approval of the final version to be published.

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