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

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Summary

Background Chimeric antigen receptor (CAR) T-cell therapy is a promising option for patients with heavily treated multiple myeloma. Point-of-care manufacturing can increase the availability of these treatments worldwide. We aimed to assess the safety and activity of ARI0002h, a BCMA-targeted CAR T-cell therapy developed by academia, in patients with relapsed or refractory multiple myeloma.

Methods CARTBCMA-HCB-01 is a single-arm, multicentre study done in five academic centres in Spain. Eligible patients had relapsed or refractory multiple myeloma and were aged 18–75 years; with an Eastern Cooperative Oncology Group performance status of 0–2; two or more previous lines of therapy including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody; refractoriness to the last line of therapy; and measurable disease according to the International Myeloma Working Group criteria. Patients received an initial fractionated infusion of 3×10^6 CAR T cells per kg bodyweight in three aliquots ($0\cdot3$, $0\cdot9$, and $1\cdot8\times10^6$ CAR-positive cells per kg intravenously on days 0, 3, and 7) and a non-fractionated booster dose of up to 3×10^6 CAR T cells per kg bodyweight, at least 100 days after the first infusion. The primary endpoints were overall response rate 100 days after first infusion and the proportion of patients developing cytokine-release syndrome or neurotoxic events in the first 30 days after receiving treatment. Here, we present an interim analysis of the ongoing trial; enrolment has ended. This study is registered with ClinicalTrials.gov, NCT04309981, and EudraCT, 2019-001472-11.

Findings Between June 2, 2020, and Feb 24, 2021, 44 patients were assessed for eligibility, of whom 35 (80%) were enrolled. 30 (86%) of 35 patients received ARI0002h (median age 61 years [IQR 53–65], 12 [40%] were female, and 18 [60%] were male). At the planned interim analysis (cutoff date Oct 20, 2021), with a median follow-up of $12\cdot1$ months (IQR $9\cdot1$–$13\cdot5$), overall response during the first 100 days from infusion was 100%, including 24 (80%) of 30 patients with a very good partial response or better (15 [50%] with complete response, nine [30%] with very good partial response, and six [20%] with partial response). Cytokine-release syndrome was observed in 24 (80%) of 30 patients (all grade 1–2). No cases of neurotoxic events were observed. Persistent grade 3–4 cytopenias were observed in 20 (67%) patients. Infections were reported in 20 (67%) patients. Three patients died: one because of progression, one because of a head injury, and one due to COVID-19.

Interpretation ARI0002h administered in a fractioned manner with a booster dose after 3 months can provide deep and sustained responses in patients with relapsed or refractory multiple myeloma, with a low toxicity, especially in terms of neurological events, and with the possibility of a point-of-care approach.

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Introduction

The survival of patients with multiple myeloma has improved as a result of the incorporation of the combination of proteasome inhibitors, immunomodulating agents, and anti-CD38 monoclonal antibodies into the standard of care since 2008. 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 multiple myeloma.[1,2]

Chimeric antigen receptor (CAR) T-cell therapy has emerged as a promising option for relapsed or refractory multiple myeloma. Several CAR T-cell products targeting BCMA using different approaches in terms of origin of

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Research in context

Evidence before this study

Effective therapies with acceptable safety profiles are needed to improve outcomes of patients with relapsed or refractory multiple myeloma, particularly for patients with disease that is refractory to immunomodulatory drugs, proteasome inhibitors, and anti-CD38 monoclonal antibodies, who have few treatment options available. We searched PubMed on Feb 15, 2023, for publications in English, with no date restriction, using the keywords "myeloma", "B-cell maturation antigen", "chimeric antigen receptor T (CART)" AND "fractionated dose" OR "booster dose". Although multiple trials assessing BCMA-targeted chimeric antigen receptor (CAR) T-cell therapies and related adoptive cellular approaches are available, we found no published studies that used a fractionated dose or a booster dose.

Added value of this study

In this single-arm, multicentre study using ARI0002h (an autologous CAR T-cell product targeting BCMA that is under development at Hospital Clinic de Barcelona, an academic institution in Spain), a fractionated dose of ARI0002h followed by a booster dose 100 days later led to early, deep, and durable responses in adult patients with relapsed or refractory multiple myeloma who had received at least two previous treatment regimens, including a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 monoclonal antibody. This trial reports novel findings in the field of immunotherapy for multiple myeloma. First, we reduced the potential immunogenicity of the CAR by using a humanised single-chain variable fragment for the recognition of BCMA, instead of one of full animal origin (mouse or llama), as is the case for the already approved commercial CAR T cells. Second, we lowered toxicity by using a fractionated administration scheme— no cases of neurotoxicity were observed. Third, a second dose was planned after 100 days in patients with response and no relevant toxicity, providing fresh and active CAR T cells to consolidate or deepen the response. Finally, this trial incorporated the concept of point-of-care treatment in cellular therapy, showing that a strategy based on two production sites and five treating hospitals is possible in a public health system.

Implications of all the available evidence

ARI0002h is a viable treatment option for patients with relapsed or refractory multiple myeloma, with an activity and safety profile comparable to approved CAR T-cell products. A point-of-care strategy to facilitate real access and administration of the product is crucial, given limited patient access to these treatments in the USA and Europe because of the lack of manufacturing capacity and reimbursement.

the antigen-recognition domain (murine, humanised, human, or llama), co-stimulatory domain (4-1BB and CD28), and transduction method (lentiviral, retroviral, or transposon)[3] are under clinical investigation. Nevertheless, only two BCMA CAR T-cell therapies, idecabtagene vicleucel and ciltacabtagene autoleucel, have been approved by the US Food and Drug Administration after at least four previous lines of therapy and the European Medicines Agency after at least three for the treatment of multiple myeloma, including proteasome inhibitors, immunomodulating agents, and anti-CD38 monoclonal antibodies.[4,5] The idecabtagene vicleucel study reported an overall response rate of 73%, with 33% of patients having complete responses (26% stringent complete responses), with a median progression-free survival of 8·8 months (95% CI 5·6–11·6) and some expected CAR T cell-related adverse events: cytokine-release syndrome in 107 (84%) of 128 patients (5% grade ≥3), immune effector cell-associated neurotoxicity syndrome (ICANS) in 23 (18%; 3% grade ≥3), and cytopenias (neutropenia 117 [91%], anaemia 89 [70%], and thrombocytopenia 81 [63%]).[6] In a phase 3 clinical trial, idecabtagene vicleucel showed improved responses and progression-free survival compared with standard care in patients exposed to three families of drugs: proteasome inhibitors, immunomodulating agents, and anti-CD38 antibodies.[7] The 2-year update[8] of the ciltacabtagene autoleucel phase 3 trial showed an overall response rate of 97·9%, with 82·5% being stringent complete responses in 97 patients with multiple myeloma treated with $0{\cdot}75\times10^6$ CAR T cells per kg bodyweight. Median progression-free survival and overall survival were not reached after a median follow-up of 27·7 months. Cytokine-release syndrome was reported in 92 (95%) of 97 patients (4% grade ≥3) and neurotoxicity in 20 (21%; nine [9%] grade ≥3), including both ICANS and other neurotoxicities. Parkinsonism symptoms occurred in six (6%) patients, with one related death and two deaths due to other causes. Parkinsonism-like neurotoxicity decreased to less than 1% after patient management strategies.[9] A study[10] of the first allogeneic BCMA-CAR T-cell therapy (ALLO-715) reported an overall response rate of 71%, including 25% or more with complete response, with a very short median time (5 days [range 0–20]) from enrolment to lymphodepletion.

Our academic institution developed two CAR T-cell 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-positive malignancies led to its approval as hospital exemption in Spain in February, 2021, making it the first academic CAR T-cell therapy in clinical use in Europe to our knowledge.[11–13] 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 that study was not specifically designed to compare outcomes of a fractionated versus non-fractionated infusion.[12,14]

ARI0002h is a humanised 4-1BB-based BCMA-CAR T-cell therapy, lentivirally transduced on autologous T cells obtained by peripheral blood leukapheresis, that has proven antitumour activity in preclinical in vitro and in vivo approaches.[15] We aimed to investigate the safety and activity of ARI0002h in patients with relapsed or refractory multiple myeloma after an initial fractionated infusion and a non-fractionated booster dose, administered at least 3 months after the first infusion in patients with some degree of response and no limiting side-effects.

Methods

Study design and participants

CARTBCMA-HCB-01 is a single-arm, open-label study done in five academic centres in Spain. Eligible patients had relapsed or refractory multiple myeloma; were aged 18–75 years; had an Eastern Cooperative Oncology Group performance status of 0–2; two or more previous lines of therapy including a proteasome inhibitor, an immunomodulating agent, and an anti-CD38 antibody; refractoriness to the last line of therapy; and measurable disease (serum and urine monoclonal protein >10 g/L or 200 mg/24 h and involved free light chain >100 mg/L) according to the International Myeloma Working Group (IMWG) criteria;[16] 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 below 50 mL/min. The full list of exclusion criteria, study protocol, and participating sites are summarised in the appendix (pp 2–5).

Patients provided written informed consent. The study protocol was approved by the Ethics Committee of Hospital Clínic de Barcelona and was done in accordance with the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects.

Procedures

Clinical coordination and vector viral production were done in Hospital Clínic de Barcelona (Barcelona, Spain). Two centres were responsible for CAR T-cell production: Hospital Clínic de Barcelona and Clínica Universidad de Navarra (Pamplona, Spain; appendix p 6). Three CAR T development strategies were adopted to improve outcomes. Firstly, the murine single-chain variable fragment (scFv), obtained from the J22.9 antibody, was humanised to reduce immunogenicity. We did preclinical experiments to show non-inferiority between constructs containing the humanised scFv versus murine scFv.[15] Second, the first dose was fractioned into 3 aliquots to reduce toxicity. Finally, we planned a second infusion (booster dose) of ARI0002h at least 3 months after the first infusion, as an experimental attempt to improve CAR T-cell persistence and response. Patient characteristics, including sex, were defined by electronic medical records. Race and ethnicity data were not collected. We assessed patients for eligibility and proceeded to leukapheresis in their respective centres. Fresh apheresis products were sent to one of the two production centres. The target dose was 3×10^6 CAR-positive cells per kg bodyweight for the first infusion and a second dose of up to 3×10^6 CAR-positive cells per kg was also obtained, when possible. The final product was cryopreserved.

Bridging therapy was allowed in the period between apheresis and lymphodepletion according to investigator's choice. Lymphodepletion was administered intravenously on days –6 to –4 (before infusion) and included fludarabine (30 mg/m²/day; total dose 90 mg/m²) and cyclophosphamide (300 mg/m²/day; total dose 900 mg/m²). The first CAR T infusion was split into three administrations of 0·3 (10%), 0·9 (30%), and $1{\cdot}8\times10^6$ (60%) CAR-positive cells per kg intravenously on days 0, 3, and 7, with at least 24 h between doses in all cases. If adverse events occurred between administrations, remaining doses were adjusted until resolution. The booster dose of up to 3×10^6 CAR-positive cells per 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 grade 3–4 cytokine-release syndrome or ICANS and other adverse events of interest (persistent cytopenias or macrophage activation syndrome). Lymphodepletion was readministered with the same scheme only in patients without CAR T-cell persistence in peripheral blood.

We followed up patients for 36 months, or until progression or death. Patients could be removed from the study on the basis of patient decision. Laboratory monitoring was planned in the following days and months from infusion: days 1, 10, 14, 21, 28, 35, 42, 56, 70, 84, and 100; and months 4, 6, 7, 8, 9, 10, 11, 12, 15, 18, 21, 24, 27, 30, 33, and 36. Bone marrow aspirates assessing measurable residual disease by next generation flow cytometry at a sensitivity of 1×10^{-6} were planned on days 28 and 100 and months 6, 12, 18, and 24. Assessment was done using two-tube eight-colour flow cytometry according to the EuroFlow platform, using a FACSCanto (BD Biosciences, [San Jose, CA, USA]) flow cytometer and Infinicyt 2.0 software (Cytognos SL, Salamanca, Spain; appendix p 7). We considered any detectable level of measurable residual disease greater than 1×10^{-6} to be positive. PET-CT scans were planned at screening and on day 100 and month 12 to assess plasmacytomas. Multiple myeloma disease evaluation was planned on days 28, 56, and 100; and months 4–12, 15, 18, 21, 24, 27, 30, 33, and 36. Responses were assessed according to IMWG criteria (appendix pp 6–7).[17] Adverse events were monitored in all follow-up visits, including a daily monitoring from day of infusion until hospital discharge. Cytokine-release

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syndrome and ICANS were assessed according to the American Society for Transplantation and Cellular Therapy consensus.[18] Intravenous immunoglobulins could be administered according to local guidelines when IgG concentrations were below 400 mg/dL.

Samples were obtained from peripheral blood and bone marrow for correlative studies (appendix p 10). BCMA expression on bone marrow plasma cells was measured by flow cytometry (PE anti-human CD269 [BCMA] antibody; Biolegend [San Diego, CA, USA]) at baseline and in measurable residual disease-positive disease. Molecules of BCMA were quantified using the BD QuantiBRITE Beads (BD Biosciences; molecules/cell). The kinetics of ARI0002h in the peripheral blood were measured by quantitative PCR (qPCR) assessing the time course of vector transgene Woodchuck Hepatitis Virus Posttranscriptional Regulatory Element to elucidate the number of ARI0002h copies per cell. Inmunogenicity against ARI0002h was assessed by flow cytometry on Attune Next (Invitrogen, Thermofisher Scientific [Waltham, MA, USA]) flow cytometer to assess the presence of human anti-human antibodies in the peripheral blood (appendix pp 8-9).

Outcomes

The primary safety endpoint was the proportion of patients who developed cytokine-release syndrome, ICANS, or both in the first 30 days after ARI0002h administration. The primary activity endpoint was overall response rate in the first 100 days of infusion, defined as achievement of at least partial response.[17] Secondary endpoints were complete response rates at 100 days and 6 months from infusion, overall response at 6 and 12 months, time to best response and time to complete response, measurable residual disease negativity rates at day 100 and month 6, plasmacytoma assessment by PET-CT at day 100, duration of response, progression-free survival, progression-free survival at 12 months, overall survival, 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, ARI0002h persistence, BCMA expression, and soluble BCMA. Quality-of-life assessment was also prespecified in the protocol but results are not provided since data are not available. Duration of response was defined as the time between first response and disease progression. Progression-free survival was defined as the time between infusion of ARI0002h and disease progression or death. Overall survival was defined as the time between infusion of ARI0002h and death due to any cause. Time to best response was defined as time between infusion and deepest response achieved according to IMWG response criteria. Time to complete response was defined as time between infusion and achievement of complete response in applicable patients.

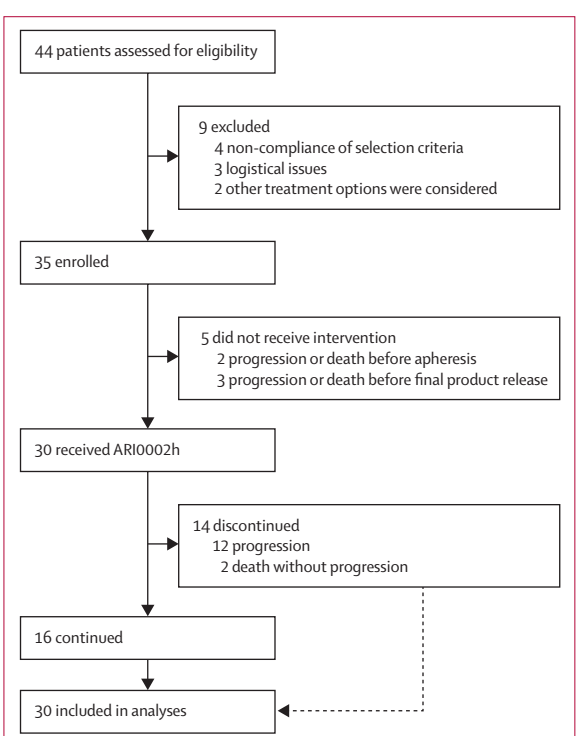

Figure 1: **Trial profile**

Statistical analysis

We initially proposed to recruit patients with the objective to treat 30 patients. We assumed that some patients would not be treated with ARI0002h because of early progression before or after apheresis. We estimated a pre-treatment patient loss of 20%; therefore, we reasoned that 36 patients would be necessary to achieve the 30 administrations expected. Sample size calculation was not done. Response analyses were done in all patients who received at least one fraction of ARI0002h. We had two hypotheses: (1) overall response rate in the first 100 days would be at least 80%, which would allow us to rule out with 95% confidence that the real overall response rate is below 65% in a population similar to the one studied; and (2) overall response rate in the first 100 days would be at least 70%, which would allow us to rule out with 95% confidence that the real overall response rate is below 54% in a population similar to the one studied.

The analysis population for safety was patients who received at least one cycle of lymphodepletion.

Here, we present results of the planned interim analysis with a cut-off date of Oct 20, 2021 to initiate regulatory review by the Spanish National Competent Authority (SNCA) and thus receive authorisation for hospital exemption. Interim data is provided to the Spanish National Competent Authority for the rolling review on a periodic basis, including information regarding safety and activity after the administration of the booster dose. At the cut-off date of the planned

	Patients treated with ARI0002h (n=30)
Age, years	61 (53–65)
Sex	
Female	12 (40%)
Male	18 (60%)
Median time since diagnosis, years	4·7 (3·7–9·1)
Heavy chain isotype	
IgG	14 (47%)
IgA	8 (27%)
Bence Jones	7 (23%)
IgD	1 (3%)
Light chain isotype	
κ	15 (50%)
λ	15 (50%)
ISS stage	
I	5/25 (20%)
II	8/25 (32%)
III	12/25 (48%)
ECOG performance status	
0	18/29 (62%)
1	9/29 (31%)
2	2/29 (7%)
Plasmacytomas	14 (47%)
Extramedullary plasmacytomas	6 (20%)
High-risk cytogenetics*	10 (33%)
TP53 alterations	7 (23%)
t(4;14)	4 (13%)
t(14;16)	1 (3%)
Number of previous lines	3·5 (2·8–5·0)
Triple exposed†	30 (100%)
Triple refractory†	20 (67%)
Penta exposed‡	11 (37%)
Penta refractory‡	7 (23%)
(Table 1 continues in next column)	
(Continued from previous column)	
Refractory to the last line	30 (100%)
Previous drug exposure	
Bortezomib	30 (100%)
Carfilzomib	15 (50%)
Ixazomib	2 (7%)
Lenalidomide	30 (100%)
Lenalidomide refractory	22 (73%)
Thalidomide	17 (57%)
Pomalidomide	17 (57%)
Daratumumab	30 (100%)
Daratumumab refractory	27 (90%)
Previous autologous stem-cell transplantation	28 (93%)
Previous allogeneic stem-cell transplantation	4 (13%)
Previous autologous and allogeneic stem-cell transplantation	4 (13%)
Bone marrow plasma cells	11·0% (1·0–32·5)
Serum monoclonal protein, g/L	12·5 (0–30·4)
Urine monoclonal protein, g/24 h	0·08 (0–1·08)
Differential sFLC, mg/L	443·2 (154·9–1144·7)

Data are n (%), n/N (%), or median (IQR). ECOG=Eastern Cooperative Oncology Group. ISS=international staging system. sFLC=serum free light chain. *Some patients had more than one high-risk cytogenetic abnormality: one patient had del(17p) plus t(4;14) and another patient had del(17p) plus t(14;16). †To a proteasome inhibitor (bortezomib or carfilzomib), an immunomodulatory drug (lenalidomide or pomalidomide), and an anti-CD38 monoclonal antibody (daratumumab). ‡To bortezomib, carfilzomib, lenalidomide, pomalidomide, and an anti-CD38 monoclonal antibody.

Table 1: **Baseline characteristics of patients treated with ARI0002h**

interim analysis, general follow-up and follow-up after the booster dose was short. To provide scientifically relevant data after a longer follow-up of patients, we did also a post-hoc analysis with a cut-off date of May 15, 2022.

Duration of response, progression-free survival, overall survival, time to best response, and time to complete response were analysed using the Kaplan-Meier method. Survival calculations between independent groups were tested with the log-rank test. When appropriate (eg, for response), 95% CIs were calculated using the Wilson score method. For survival times, 95% CIs were calculated with the log method. Reasons for censoring were last follow-up without progression or death without progression for duration of response, last follow-up without progression or death for progression-free survival, and last follow-up without death for overall survival.

Post-hoc analyses of vein-to-vein time according to receipt of bridging therapy (yes or no), response and progression-free survival according to receipt of the full first dose of ARI0002h (yes or no), expansion of CAR T-cells in peripheral blood after booster dose according to receipt of lymphodepletion (yes or no), duration of response and progression-free survival according to the achievement of complete response, progression-free survival and overall survival according to the presence of plasmacytomas were done.

p values from post hoc comparisons are provided, which should be considered informative and descriptive, but not conclusive. We calculated p values of categorical variables with χ^2 or Fisher's exact test according to sample size. We calculated p values of continuous variables, including paired sample comparisons, with the Student's *t* test, Wilcoxon–Mann–Whitney, or Wilcoxon signed-rank test according to their adherence to the Gaussian distribution tested with the Saphiro–Wilk test. If appropriate, p values were adjusted for multiple comparisons with the Benjamini–Hochberg method. A p value of less than 0·05 was considered statistically significant.

Statistical analyses were done with SAS System (version 9.4) and R (version 4.3.0).

This study is registered with ClinicalTrials.gov, NCT04309981, and EudraCT, 2019-001472-11.

	Grade 1	Grade 2	Grade 3–4
Cytokine release syndrome	15/24 (63%)	9/24 (38%)	0
Immune effector cell-associated neurotoxicity syndrome	0	0	0
Infusion reaction	1/30 (3%)	0	0
Tumour lysis syndrome	0	1/30 (3%)	0
Persistent cytopenias	0	0	20/30 (67%)

Data are n (%). Adverse events of special interest are depicted per MedDRA preferred term.

Table 2: **Adverse events of special interest**

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between June 2, 2020, and Feb 24, 2021, we assessed 44 patients for eligibility (figure 1). We enrolled 35 patients, of whom 33 (94%) underwent leukapheresis and 30 (86%) received ARI0002h (figure 1). The median manufacturing time of ARI0002h was 10 days (IQR 9–10), with a mean transduction rate of 56% (SD 25). All final products for the first infusion were successfully obtained at the first attempt except one, which was produced with a second apheresis. Median turnaround time, defined as days from apheresis reception to product liberation, was 30 days (IQR 26–36; range 19–45). In a patient requiring urgent treatment, the product was released in as fast as 19 days. The median age of patients who received ARI0002h was 61 years (IQR 53–65), 12 (40%) were female, and 18 (60%) were male (table 1). 14 (47%) of 30 patients presented with plasmacytomas at inclusion, with six (20%) presenting with a true extramedullary, non-paraskeletal location (table 1). Assessment of disease before and after bridging therapy showed either no change or progression of the serum M-protein or free light chain in six patients (43%); in eight (57%) a decrease was observed, with no patients having a complete response (appendix p 11).

All 30 patients received fractions 1 and 2. Five (17%) patients did not receive the third fraction of the first dose of ARI0002h because of cytokine-release syndrome. 24 (86%) of 28 eligible patients received the second administration of ARI0002h (booster dose) in a single infusion of 100% of the dose. Two patients were not eligible for the booster dose because of extramedullary progression on day 100 (n=1) and death (cranial injury) in month 4 (n=1). Four (14%) of the 28 eligible patients did not receive the booster dose because of prolonged cytopenias, diagnosis of a secondary neoplasm, macrophage activation syndrome, and lymphocytosis due to CAR T-cell expansion (n=1 each; appendix p 12). In 19 (79%) of the 24 patients who were reinfused, 3×10^6 CAR-positive cells per kg were available for the booster dose; $1{\cdot}8\times10^6$ CAR-positive cells per kg were available for three patients and $1{\cdot}2\times10^6$ CAR-positive cells per kg were available for two patients (appendix p 12). Median time to booster dose was 4 months (IQR 3–5; range 3–7). Eight (33%) of 24 patients received a second lymphodepletion regimen before the booster dose, based on CAR T-cell detection in peripheral blood.

At the interim analysis (data cutoff Oct 20, 2021; median follow-up 12·1 months [IQR 9·1–13·5]), 10 (33%) of 30 (95% CI 19–51) patients had discontinued: eight patients developed disease progression and two died without progression (one after a cranial injury in month 4 and one after severe SARS-CoV-2 pneumonia in month 9). No discontinuations occurred due to manufacturing failures. An additional death occurred in a patient with disease progression. No deaths occurred within the first month of treatment.

Cytokine-release syndrome was observed in 24 (80%) of 30 patients, in each case after receiving at least the second fraction of 30% (total dose 40%), with no grade 3 or higher events (15 [63%] grade 1 and nine [38%] grade 2; table 2). Median time to onset of cytokine release syndrome was 7 days (IQR 5–8) from the first fraction (10%), with a median duration of symptoms of 2 days (0–14). Tocilizumab was administered in 19 (63%) of 30 patients, mainly for persistent grade 1 cytokine-release syndrome, and three (10%) patients received steroids. Because of cytokine-release syndrome, a clinical decision was made that five patients would not receive the third fraction of $1{\cdot}8\times10^6$ CAR-positive cells per kg. No cases of ICANS or late neurologic events were observed. None of the patients who received the booster dose had cytokine-release syndrome, ICANS, or any adverse events of special interest after the booster dose.

One mild infusion reaction and one moderate tumour lysis syndrome were reported (table 2). Prolonged cytopenias were reported in 20 (67%) of 30 patients (table 2). The median duration of grade 4 neutropenia was 35 days (95% CI 26–44) and time to complete resolution of cytopenias was 4 months (95% CI 3–5) for neutropenia, 12 months (6–18) for thrombocytopenia, and 3 months (1–13) for anaemia. All patients recovered without requiring a stem-cell boost. The overall safety profile is shown in table 3.

Infections were reported in 20 (67%) of 30 patients. 45 infectious episodes (seven [16%] grade ≥3) were reported, with most patients experiencing an average of 1–2 infection episodes (appendix p 13). Respiratory tract infections were the most common, with 24 (53%) episodes, including three (10%) of 30 patients having SARS-CoV-2 infections. Other relevant adverse events were a new diagnosis of colon adenocarcinoma, considered non-related to ARI0002h, and one reactivation of hepatitis B virus, considered related to ARI0002h. Three cases of macrophage activation syndrome occurred, two of them in combination with a grade 1 cytokine-release syndrome; all cases resolved completely.

Overall response rate during the first 100 days from infusion was 100%, including 24 (80%) of 30 patients with a very good partial response or better (15 [50%] with complete response, nine [30%] with very good partial response, and six [20%] with partial response). Median time to complete response was 3·8 months (IQR 1·0–11·6). On day 28, measurable residual disease by next generation flow cytometry was evaluable in 22 (73%) of 30 samples, with 21 (95% [95% CI 78–99]) patients presenting a negative result (appendix p 14). On day 100, 24 (92% [95% CI 76–98]) of 26 evaluable samples were negative (appendix p 14).

In a post-hoc analysis using a data cutoff date of May 15, 2022 (median follow-up 18 months [IQR 15–20]), the overall response rate was 100% (95% CI 89–100) with 20 patients with complete response (67% [49–81]), eight with very good partial response (27% [14–44]), and two with partial response (7% [2–21]; figure 2A). 18 (60%) of 20 patients with complete response had a stringent complete response. Responses at month 6 were 14 (47% [95% CI 30–64]) of 30 patients with complete response, 11 (37% [22–55]) with very good partial response, two (7% [2–21]) with partial response, two (7% [2–21]) with progressive disease, and one (3% [1–17]) death without relapse. Responses at different timepoints are shown in the appendix (pp 15–16). Median time to best response was 3·3 months (95% CI 1·0–3·4), with some patients improving responses after 100 days (figure 2B). The differences in overall response rate at 100 days and at this follow-up (median 18 months) show that responses deepen over time, with five (25%) of 20 patients having a complete response after month 3 (100 days), and five (17%) of 30 patients having their best response after 6 months (one converted to very good partial response and four converted to complete response; figure 2B). 20 (80%) of 25 evaluable patients were negative for measurable residual disease at 6 months, and 16 (80%) evaluable patients were negative for measurable residual disease at 12 months (appendix p 14).

14 (58% [95% CI 30–76]) of 24 patients who received the booster dose had a stringent complete response before reinfusion, six (25% [12–45]) patients maintained the response after reinfusion (all very good partial response) and four (17% [7–36]) patients had an improved response after the booster dose, two patients with very good partial response and two with partial response converted to complete response (figure 2C).

At the May 15, 2022, data cutoff date, median duration of response was not reached (95% CI 12·9–not reached; figure 3A) and median overall survival was not reached (8·0–not reached; figure 3B). Two patients died in response in months 4 and 9. 12-month overall survival was 86·5% (95% CI 75·1–99·7). Median progression-free survival was 14·5 months (95% CI 12·8–not reached; figure 3B). 14 (47%) patients had a progression-free survival event: 12 developed disease progression and two died without progression. 12-month progression-free survival was 70% (95% CI 55–89).

	Grade 1–2	Grade 3	Grade 4	Grade 5
Blood and lymphatic system disorders				
Anaemia	16 (53%)	2 (7%)	1 (3%)	0
Neutropenia	9 (30%)	8 (27%)	13 (43%)	0
Thrombocytopenia	13 (43%)	8 (27%)	6 (20%)	0
Asthenia	9 (30%)	0	0	0
Pyrexia	7 (23%)	2 (7%)	0	0
Oedema peripheral	3 (10%)	0	0	0
Febrile neutropenia	..	1 (3%)	0	0
Lymphocytosis	..	0	1 (3%)	0
Lymphopenia	..	0	1 (3%)	0
Gastrointestinal and hepatobiliary disorders				
Diarrhoea	5 (17%)	1 (3%)	0	0
Hepatobiliary disorders				
Hepatotoxicity	3 (10%)	0	0	0
Immune system disorders				
Cytokine release syndrome	24 (80%)	0	0	0
Haemophagocytic lymphohistiocytosis	3 (10%)	0	0	0
Respiratory tract infection	3 (10%)	0	0	0
Upper respiratory tract infection	6 (20%)	0	0	0
Investigations				
Hypocalcaemia	7 (23%)	0	0	0
Hypomagnesaemia	6 (20%)	0	0	0
Headache	5 (17%)	0	0	0
Back pain	4 (13%)	0	0	0
Alanine aminotransferase increased	4 (13%)	1 (3%)	0	0
Aspartate aminotransferase increased	3 (10%)	1 (3%)	0	0
Blood lactate dehydrogenase increased	3 (10%)	0	0	0
Gamma-glutamyltransferase increased	3 (10%)	0	0	0
Hypokalaemia	3 (10%)	0	0	0
Psychiatric disorders				
Anxiety	3 (10%)	0	0	0
Infections and infestations				
COVID-19	..	0	0	1 (3%)
Leishmaniasis	..	1 (3%)	0	0
Rhinovirus infection	..	1 (3%)	0	0
Septic shock	..	1 (3%)	0	0
Severe acute respiratory syndrome	..	1 (3%)	0	0
Staphylococcal bacteraemia	..	1 (3%)	0	0
Injury; poisoning and procedural complications				
Head injury	..	0	0	1 (3%)
Nervous system disorders				
Seizure	..	0	1 (3%)	0
Renal and urinary disorders				
Acute kidney injury	..	1 (3%)	0	0
Vascular disorders				
Hypertension	..	1 (3%)	0	0

For grades 1–2, only adverse events with an occurrence of 10% or more are shown. For grades 3–5, all adverse events are shown. Adverse events are reported according to Common Terminology Criteria of Adverse Events (version 5.0).

Table 3: **Adverse events (n=30)**

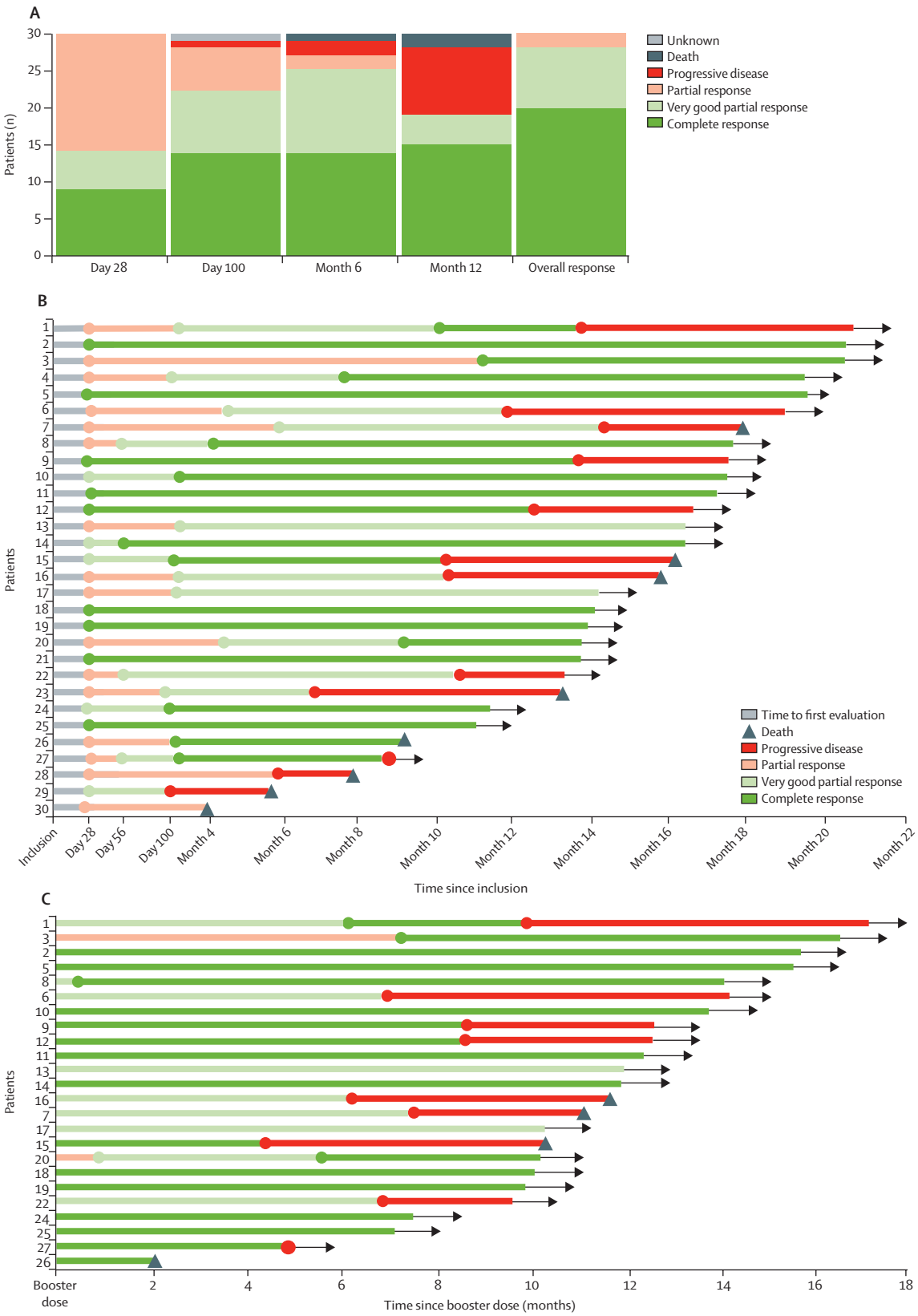

Figure 2: **Activity of ARI0002h**
(A) Overall response rate and response evaluation at consecutive timepoints. (B) Swimmer plot with the response of each individual patient after first infusion (n=30). Data cutoff was May 15, 2022. (C) Swimmer plot with the response of each patient after booster dose (n=24).

A PET-CT scan at day 100 showed a metabolic response in 13 (93% [95% CI 69–98) of 14 patients with a plasmacytoma at baseline. The six patients with plasmacytomas who had disease progression died, and all patients without plasmacytomas who had disease progression were alive at data cutoff.

ARI0002h detection in peripheral blood by PCR showed a median persistence of 5·0 months (95% CI 3·8–6·2). 15 (52%) of 29 patients with available samples on day 100, seven (28%) of 25 with available samples at month 6, and four (20%) of 20 with available samples at month 12 had detectable CAR T cells in peripheral blood (appendix p 19). The peak of expansion was observed on day 14 for most patients (range 7 days to 6 months; appendix p 20). Mean copies per genome at the peak of expansion were 11·1 (SD 14·2). Nine (75%) of 12 patients with an available sample at relapse, three (33%) still had detectable CAR T cells in peripheral blood.

After the booster dose, 12 (50%) of 24 patients presented a low-grade expansion of CAR T cells immediately after administration, with a mean peak of 4·0 copies per genome (SD 9·2; appendix p 20). In a post-hoc analysis, we found no correlation between previous lymphodepletion and expansion of CAR T cells (three [38%] of eight patients receiving lymphodepletion expanded *vs* nine [56%] of 16 without lymphodepletion; p=0·67).

The mean number of BCMA molecules per cell on malignant bone marrow plasma cells by flow cytometry at inclusion was 1306·5 (SD 889·1). The change in the number of BCMA molecules per cell in six paired samples available at relapse showed a decrease from mean 1784 (1229·8) molecules per cell to 1001·5 (916·1) molecules per cell (p=0·054). None of the six samples had a complete loss of BCMA expression. Soluble BCMA was detectable in peripheral blood 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 soluble BCMA at the end-of-treatment sample (appendix p 21).

Positivity of human anti-human antibodies was not sustained for each individual patient (appendix p 22). We detected human anti-human antibodies in 21 (70%) of 30 patients (appendix p 22). Eight (25%) of 12 patients who relapsed had available human anti-human antibody measurements, of whom only two (25%) were positive.

In a post-hoc analysis, median vein-to-vein time was 43 days (IQR 35–54), with differences among patients who did or did not receive bridging therapy (54 days [IQR 44–58] *vs* 36 days [IQR 30–43]; p=0·0006). We found no differences in response rates or progression-free survival between patients who received only the first two fractions of the first dose versus those who received the full first dose (complete response: three [60%] of five *vs* 17 [68%] of 25; p=0·73; median progression-free survival: 14·5 months [95% CI 12·8–not reached] *vs* not reached [12·1–not reached]; p=0·83; post-hoc analysis). In a post-hoc

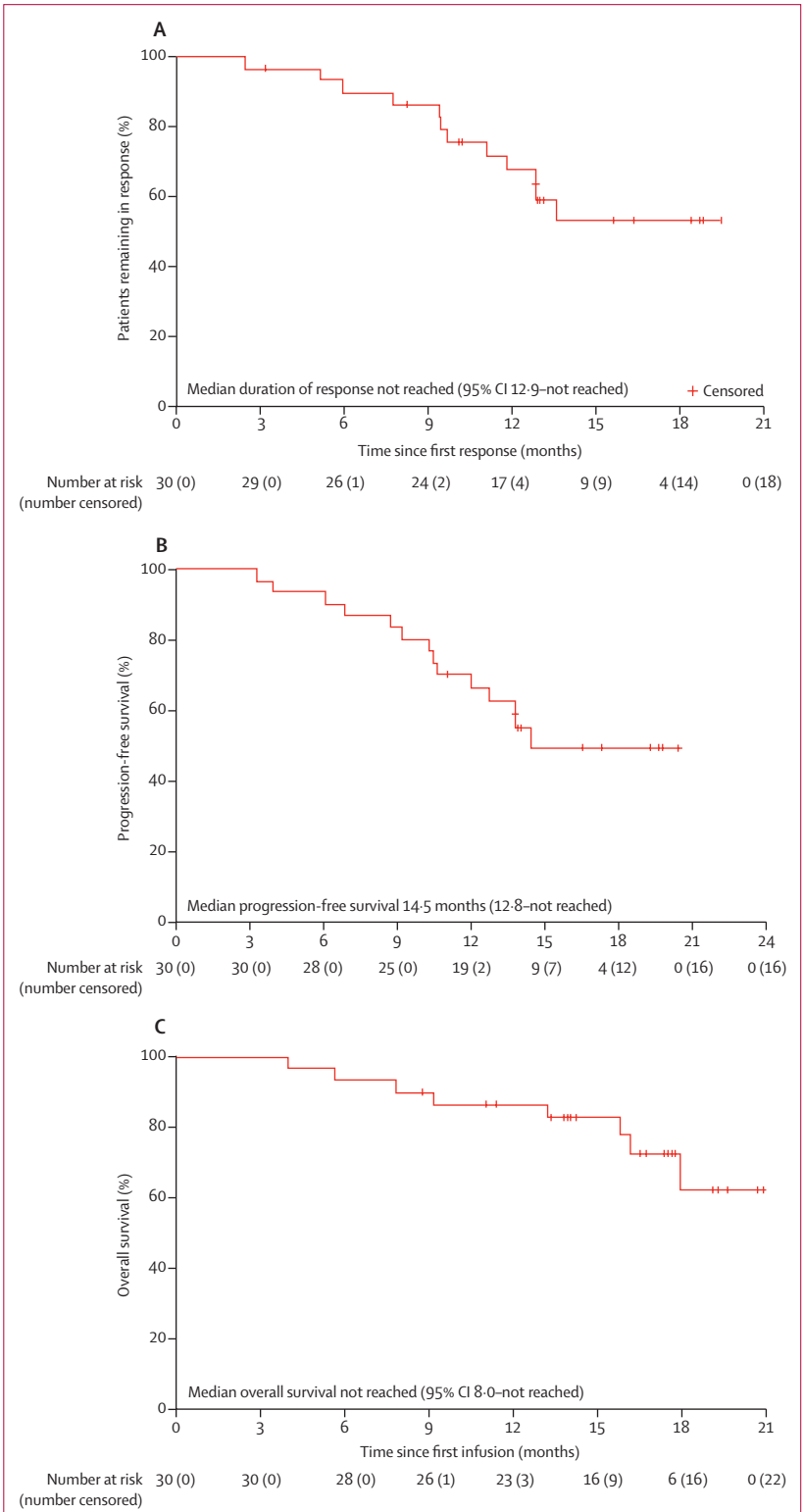

Figure 3: **Duration of response and survival of patients treated with ARI0002h**
(A) Duration of response (n=30). (B) Progression-free survival. (C) Overall survival. Median follow-up for survival was 18 months (IQR 15–20). Data cutoff was May 15, 2022.

analysis, median duration of response in patients who had a complete response was not reached (95% CI not reached–not reached) versus 9·7 months (6·0–not reached) in those who did not have a complete response (p=0·0041; appendix p 17). No differences in terms of progression-free survival or overall survival were detected according to the presence or absence of plasmacytomas at inclusion (post-hoc analysis; appendix p 18).

Discussion

CAR T-cell therapy is a promising option for patients with heavily treated relapsed or refractory multiple myeloma. Here, we showed that ARI0002h, a CAR T-cell therapy developed in academia and administered in a fractioned manner with the option of adding a booster dose after day 100, can provide deep and sustained responses with low-grade toxicity in patients with a poor prognosis. In this study, all treated patients had at least a partial response, with good results in terms of measurable residual disease negativity as early as day 28 after treatment. The development of cytokine release syndrome with ARI0002h was similar to that of other BCMA-CAR T-cell therapies, showing a lower grade of severity, with none grade 3 or above and no cases of ICANS or late neurotoxicity. Therefore, ARI0002h might be a reasonable alternative to other BCMA CAR T-cell constructs,[3] including the already approved idecabtagene vicleucel and ciltacabtagene autoleucel. 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-positive malignancies.[12] Other factors, such as construct features, manufacturing process, and total cell-dose administered might also play an important role in safety. Patients who received only two fractions of the first dose showed similar outcomes compared with those receiving the full dose. Patients who received only two fractions of the first dose developed an early cytokine-release syndrome, probably reflecting a fast in vivo expansion of the CAR T-cell therapy, which might explain the similar outcome to that of those who received the full first dose. Prolonged cytopenias and infections were a common adverse event, with a similar profile to that reported in other BCMA-CAR T-cell studies.[6,9] A study[9] of ciltacabtagene autoleucel reported infections in 56 (58%) of 97 patients and a retrospective analysis showed 47 infection events in 29 (53%) of 55 patients after BCMA CAR T-cell therapy.[19]

Some patients with multiple myeloma might have soft-tissue involvement in the form of paraskeletal or extramedullary plasmacytomas. The treatment of these patients is a highly unmet need because available treatments have poor efficacy.[20] The progression-free survival of patients treated with ARI0002h according to soft-tissue involvement at inclusion did not differ significantly, highlighting the positive effect that CAR T-cell therapy might have in this subgroup of patients with multiple myeloma.[6,21]

The incorporation of a second infusion of ARI0002h 100 days after the first administration was meant 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.[22,23] In terms of activity, four out of ten patients with measurable disease had an improved response after the booster dose. Because there was no comparator group in this trial, we cannot affirm that these results are only attributable to the second infusion. In other BCMA-CAR T-cell trials,[6,9] a deepening of responses over time has been reported. However, median time to best response reported in the ciltacabtagene autoleucel study was 2·6 months,[9] suggesting that most patients had the deepest response within the first 3 months. Although the booster dose might play a role in improving and lengthening responses, this association is difficult to establish in this non-randomised trial, especially as 14 of 24 patients already had complete responses at the time they received the 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 and a randomised study exploring this feature could be helpful to clarify the efficacy of this approach.

Despite promising results, patients continued to relapse after treatment with ARI0002h; therefore, strategies to overcome relapses are of pertinent interest. Correlative studies done on patient samples highlight different mechanisms that might be responsible for relapse after ARI0002h treatment. A median persistence of CAR T cells in peripheral blood of 5 months, although similar to that of other available BCMA-CAR T cells, is still short (idecabtagene vicleucel reported persistence in 59% of patients at 6 months and 36% at 12 months and most ciltacabtagene autoleucel patients had transgene concentrations below the threshold of quantification at 6 months).[6,9] The short duration of CAR T-cell persistence in peripheral blood contrasts with long response durations in terms of progression-free survival. BCMA quantification on malignant plasma cells decreased from baseline levels in most patients, but no patients became BCMA negative and soluble BCMA was positive in all patients at relapse. Finally, several patients had detectable CAR T cells at relapse, suggesting that CAR T-cell exhaustion with increase of some surface markers[24] could play a role in shortening duration of responses.

Demand for CAR T-cell therapy is increasing, and it will presumably be introduced into earlier lines of treatment.[25] However, high costs, manufacturing delays, and potential bottlenecks of centralised, industry-driven CAR T-cell production can limit access to this therapy.[26–28] Additionally, despite the European Commission authorisation for

idecabtagene vicleucel and ciltacabtagene autoleucel, the products are not available in Spain and several other European countries because no reimbursement agreement exists. ARI0002h is an academic CAR T-cell therapy that has been manufactured in two facilities in Spain, being a real point-of-care manufacturing approach in these two centres (Barcelona and Pamplona). This approach can increase the number of slots available for production, allowing a fast release when required by the clinical situation of the patient; in our study, this was as short as 19 days. ARI0002h can be manufactured at up to a quarter of the cost of that of commercial CAR T cells. For these reasons, we believe that CAR T cells produced at academic institutions will become essential to improve access around the world.

Contributors

AO-C, BM-A, LR, NT, RJ, SV, JS-P, JD, MJ, MP, AU-I, and CFdL participated in conception and design of the work. AO-C and ME-R participated in the writing of the manuscript draft. AO-C, VG-C, VC, PR-O, JLR, LL-C, AZ, BP, SI, AL-DdC, ML-P, AS-S, JAP-S, FP, JMM, and M-VM provided data and figures. AO-C, VG-C, VC, PR-O, JLR, L-LC, AZ, BP, SI, AL-DdC, ML-P, and CFdL contributed to data collection. AO-C, ME-R, AZ, BP, SI, AL-DdC, LGR-L, SV, and JS-P performed data analysis and interpretation. AOC and CFdL have verified the data. All authors revised the article and gave approval of the final version to be published.

Declaration of interests

AO-C declares support for attending meetings from Janssen. VG-C declares receiving honoraria from Janssen, Pfizer, Bristol Myers Squibb (BMS)/Celgene, and GSK; support for attending meetings or travel from Janssen and GSK; and 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; and 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; and 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; and 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; and participation on data safety monitoring or advisory board from Janssen. BM-A declares to be co-inventor 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; and 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; and 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, and advisory fees with Gilead, Jazz, Alexion, AMGEN, Novartis, Janssen, BMS, and MSD; and 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; and 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; and a leadership or fiduciary role in RICORS Terav and IDISNA. MJ declares receiving research or travel support by Fundació Bancaria la Caixa, ISCIII, and CellNex Teleom; honoraria from educational activities, speaker, and advisory roles with Miltenyi and indirectly with sponsors of congresses; and participation on data safety monitoring or advisory boards with MAB Gyala. JMM declares receiving honoriaria from Gilead/Kite, Novartis, BMS/Celgene, and Roche; travel grants, accommodation, and expenses from Jazz Pharma, Gilead-Kite, Janssen, and Sandoz; and consulting or advisory board fees in Jazz Pharma, Novartis, and Sandoz. M-VM declares honoraria derived from lectures and participation in advisory boards from Janssen, BMS/Celgene, Takeda, Amgen, GSK, Pfizer, Regeneron, Roche, and Sanofi. MP declares receiving honoraria from Thermofisher Scientific and LetiPharma. AU-I declares receiving grants from the Spanish Ministry of Health (ISCIII); honoraria for lectures from BMS and Gilead; support for attending meetings from Amgen; 23% of participation in ARI-002 patent ARI-001 patent in preparation; advisory board fees and participation in Miltenyi biomedicine; being coordinator of the Spanish group of CAR T-cell therapy. CFL declares receiving grants through his institution from BMS, Janssen, and Amgen; honoraria from Amgen, Janssen, BMS, GSK, and Sanofi; support for attending meetings or travel from Janssen, BMS, GSK, and Amgen; and participation in data safety monitoring or advisory boards with Janssen, BMS, Amgen, Pfizer, and Sanofi. All other authors declare no competing interests.

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. Additional related documents are available at https://clinicaltrials.gov/ct2/show/NCT04309981.

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