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ORAL ABSTRACTS

704.CELLULAR IMMUNOTHERAPIES: EARLY PHASE AND INVESTIGATIONAL THERAPIES

ARI0002h (Cesnicabtagene Autoleucel), an Academic Point-of-Care B-Cell Maturation Antigen (BCMA)-Directed Chimeric Antigen Receptor (CAR) T-Cell Strategy: Activity and Safety after Fractionated Initial Therapy and Booster Dose in 60 Patients with Relapsed/Refractory Multiple Myeloma

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Background: We reported the safety and activity ofARI0002h, an academic autologous 4-1BB-based CAR T-cell product with a humanized scFv targeting BCMA in a pilot multicenter clinical trial (CARTBCMA-HCB-01) in 30 patients (pts) with relapsed/refractory multiple myeloma (RRMM) (NCT04309981) (Oliver-Caldés, Lancet Onc 2023). Here, we report results of 30 additional pts (cohort 2) and a longer follow-up of cohort 1.

Methods: Pts aged 18-75 years old with RRMM were eligible if they had measurable disease, received ≥2 prior regimens, including a proteasome inhibitor, an immunomodulatory drug and an anti-CD38 antibody, and were refractory to the last line of treatment. Bridging therapy was allowed after apheresis. Lymphodepletion (LD) with cyclophosphamide and fludarabine was used. The target dose (3x10^6/kg CAR+cells) was administered in a fractionated manner (10%/30%/60%), with at least 24h between infusions. A second dose of up to 3x10^6 CAR+ cells/kg was planned at least 3 months after the first dose in pts with any kind of response and no limiting side effects; LD was repeated according to CAR-T cell persistence. Primary endpoints were overall response rate (ORR) within the first 3 months and rate of cytokine release syndrome (CRS) and/or neurotoxicity

in the first 30 days. Response was assessed as per IMWG criteria and bone marrow minimal residual disease (MRD) was analyzed by next-generation flow at a sensitivity of 10^{-6}. CART persistence in the peripheral blood (PB) was measured by PCR. Adverse events were graded using CTCAE v5.0. CRS and neurotoxicity were graded according to the American Society for Transplantation and Cellular Therapy criteria.

Results: As of March 17 th 2023, 72 pts with RRMM were screened, 69 underwent apheresis and 61 received LD, with 60 pts finally receiving ARI0002h (modified intention-to-treat population). The main features are described in Table 1. 48% required bridging therapy. Median CAR-T cell production and turnaround times were 9 days (IQR 8-10) and 32 (IQR 27-36.5), respectively. Median vein-to-vein time was 41 days (IQR 34-51), with differences between pts receiving or not bridging therapy (48 vs. 36 days; p=0.004).

The ORR in the first 3 months was 95% (≥ very good partial response (VGPR) in 77%). Median time to first response was one month. Responses deepened over time, achieving 58% complete response (CR) (55% stringent CR), 30% VGPR, 7% partial response, 1 patient (2%) was refractory and 2 pts (3%) died prior to first evaluation (septic shock and macrophage activation syndrome (MAS)). MRD-negative rates on evaluable samples on days 28 and 100 were 98% and 96%, respectively.

With a median follow-up of 23.1 months (95%CI 9.2-37.1), estimated median progression-free survival (PFS) was 15.8 months (CI95% 11.5-22.4) (Figure 1). No differences in PFS were found based on high-risk cytogenetics, plasmacytomas or triple-refractoriness. Median overall survival (OS) was not reached with OS rates at 12 and 18 months of 81% and 69%. Eighteen of 60 (30%) pts died due to disease progression (n=13), COVID19 (n=2), cranial trauma, septic shock and MAS (n=1 each).

CRS was observed in 90% with 5% grades ≥ 3. Median time to CRS was 7 days (1-14); median duration of 4.5 days. Mild ICANS was reported in only 2 pts (3%) with no late neurologic events. 6 pts (10%) developed a MAS (4 grades 1-2, 1 grade 3, 1 grade 5). Tocilizumab and steroids were administered in 68% (mainly for persistent grade 1 CRS) and 30% of pts, respectively.

44 out of 55 eligible pts (80%) had already received the booster dose, with no relevant toxicities. Median time after first infusion was 4.4 months; 34% received a second LD. Response was evaluable in 42 pts; 45% (n=19) were already in sCR, 29% (n=12) maintained the response and 26% (n=11) improved the response.

Median ARI0002h persistence in PB was 5 months (95%CI 3.0-7.0), with an expansion peak on days 14 (70%) and 28 (19%). At 3 and 6 months, 65% and 52% had measurable CART in peripheral blood, respectively, and 33% of relapsed pts had detectable CART. Increased expression of surface markers associated with exhaustion (PD1 and TIGIT) was observed in CAR+ cells between the time of the final product and day 28 (p<0.001).

Conclusion: Results from 30 additional pts and a longer follow-up of the first cohort confirm the deep and durable responses obtained with ARI0002h. The booster dose may be partially responsible for the improvement of responses over time and exhaustion may play a role in relapse.

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Table 1. Main characteristics of the patients, response and safety.

	All patients (n=60)	Cohort 1 (n=30)	Cohort 2 (n=30)
Age (years); median (range)	58 (36-74)	61 (36-74)	56 (39-73)
Sex (F/M)	26/34	12/18	14/16
Heavy chain isotype IgG/IgA/IgD/Only light chain (%)	52/27/3/18	47/27/3/23	57/27/3/13
Light chain isotype kappa/lambda (%)	55/45	50/50	60/40
ISS stage at baseline I/II/III (%)	49/23/28	32/32/36	65/14/21
Plasmacytomas (%)	50	47	53
Extramedullary location	18	20	17
Serum M protein (g/L); mean (range)	10.5 (0-90)	12.5 (0-90)	8.5 (0-39)
Bone marrow plasma cells (%); median (IQR)	13 (2-31)	15 (2-37)	13 (2-30)
High-risk cytogenetics (%)*	28	33	21
Number of previous lines; median (range)	3 (2-10)	3.5 (2-10)	3 (2-6)
Prior autologous stem cell transplantation (%)	90	93	87
Prior allogeneic stem cell transplantation (%)	8	13	3
Prior drug exposure (%) / refractoriness (%)			
Bortezomib	100/52	100/54	100/50
Lenalidomide	100/78	100/77	100/80
Anti-CD38 monoclonal antibody	100/93	100/87	100/100
Carfilzomib	57/45	50/36	63/53
Pomalidomide	52/48	60/54	43/43
Bridging therapy (%)	48	47	50
Overall response in the first 100 days (%)	95	100	90
≥ Complete response (stringent CR)	44(40)	50(43)	37(37)
Very good partial response	33	30	37
Partial response	18	20	17
Refractory	2	-	3
Death prior to evaluation	3	-	6
Measurable residual disease negative; n negative/n evaluable (%)			
Day 28	40/41 (98%)^	21/22 (95%)	19/19 (100%)^
Day 100	49/51 (96%)^	24/26 (92%)	25/25 (100%)^
Cytokine release syndrome; n, (%)	54 (90)	27 (90)	27 (90)
Grade 1-2	51 (85)	27 (90)	24 (80)
Grade ≥ 3	3 (5)	0	3 (10)
Neurotoxicity; n, (%)			
Immune-effector cell associated neurotoxicity syndrome	2 (3)	0	2 (7)
Late neurologic events	0	0	0

* del(17p), t(4;14), t(14;16); ^Three of the unavailable samples were due to: one patient was primary refractory and 2 patients died before first evaluation.

Figure 1. Median progression-free survival (n=60).

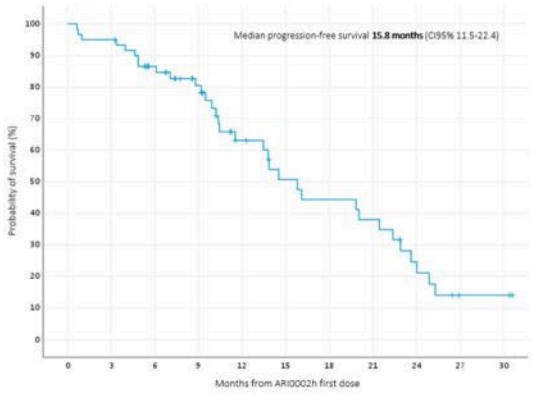

Figure 1

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