PHASE I TRIAL OF MB-CART2019.1 IN PATIENTS WITH RELAPSED OR REFRACTORY B CELL NON-HODGKIN LYMPHOMA: 2-YEAR FOLLOW-UP REPORT

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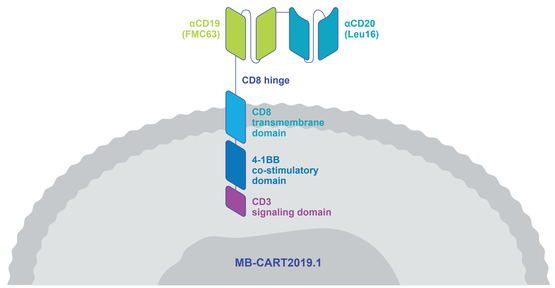
Introduction

- Approved cluster of differentiation (CD)19 chimeric antigen receptor (CAR) T cell products have demonstrated excellent response rates in patients with diffuse large B cell lymphoma (DLBCL); however, not all patients show durable benefit from currently approved CAR T cell therapies, indicating a significant unmet medical need for further improvements[1–3]
- Relapses after CD19-directed CAR T cell therapy occur in 40–50% of patients, possibly due to CD19 antigen escape and T cell exhaustion[4,5]
- Targeting a single B cell antigen may lead to selective pressure with antigen escape and subsequent relapse.[1,6] Thus, targeting more than one antigen may result in improved efficacy by reducing potential downregulation of cell surface markers and subsequent relapse
- MB-CART2019.1 is an *ex vivo*-generated, bispecific tandem CAR T cell consisting of autologous CD4 and CD8 enriched cells, which are transduced with a lentiviral vector that encodes the CAR construct for both CD20 (Leu16) and CD19 (FMC63) single chain variable fragments sequentially linked to each other, and incorporating a 4-1BB co-stimulatory domain and a CD3ζ signaling domain (**Figure 1**)
- Zamtocabtagene autoleucel is the recommended international nonproprietary name for MB-CART2019.1

Figure 1. Illustration of the CAR construct for MB-CART2019.1



CAR, chimeric antigen receptor; CD, cluster of differentiation

Aim

This study (DALY 1: NCT03870945) aimed to assess the feasibility, toxicity, and safety of MB-CART2019.1 in patients with relapsed or refractory (r/r) CD20 and CD19 positive B cell non-Hodgkin lymphoma (B-NHL). Here, we report the results from the 2-year follow-up analysis

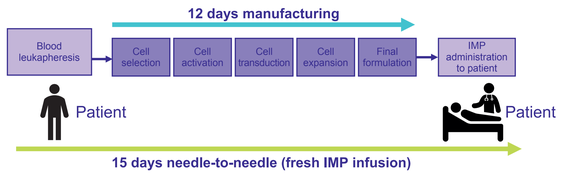
Methods

Study design

DALY 1 is a prospective, first-in-human, multicenter, open-label, Phase I/II trial assessing the feasibility, dosage, safety, and toxicity, as well as preliminary evidence of response to treatment, of MB-CART2019.1 in B-NHL

- Patients received one of two predefined dose levels (DL) as follows:
  - DL1: 1.0 × 10^6 CAR T cells/kg body weight (BW)
  - DL2: 2.5 × 106 CAR T cells/kg BW
- Lymphodepletion:
  - DL1: fludarabine (30 mg/m2 Day -5 to -3); cyclophosphamide (300 mg/m2 Day -5 to -3)
  - DL2: fludarabine (30 mg/m2 Day -5 to -3); cyclophosphamide (500 mg/m2 Day -5)

Figure 2. Manufacturing and infusion of MB-CART2019.1



IMP, investigational medicinal product

Study population and patient characteristics

- Patients were eligible if they had:
  - DL1: CD20 and CD19 positive, r/r B-NHL without curative treatment options
  - DL2: r/r DLBCL and 1 prior line of therapy, ineligible for high-dose chemotherapy and stem cell transplantation
- Baseline characteristics for the overall population are shown in **Table 1**

Endpoints

- Primary endpoint: maximum tolerated dose (MTD) of MB-CART2019.1 defined as the highest DL at which <33% of patients experience dose-limiting toxicity (DLT) until Day 28 after infusion of MB-CART2019.1
- Secondary endpoints: objective response rate (ORR), duration of response, adverse events (AEs), maximum concentration (C_{max}), area under the curve ($AUC_{d0\text{-}d28}$), and persistence of CAR T cells measured by flow cytometry

Table 1. Patient demographics and disease characteristics

Characteristics	Dose level 1 (N=6)	Dose level 2 (N=6)	Total (N=12)
Age, years			
Median (range)	68 (20–73)	75 (71–78)	72 (20–78)
Gender, n (%)			
Male	4 (67)	3 (50)	7 (58)
Female	2 (33)	3 (50)	5 (42)
Diagnosis at screening, n (%)			
DLBCL, NOS	3 (50)	5 (83)	8 (67)
DLBCL, PMBCL	1 (17)	0	1 (8)
DLBCL, TFL	1 (17)	1 (17)	2 (17)
MCL	1 (17)	0	1 (8)
Refractory participants, n (%)			
Yes	3 (50)	3 (50)	6 (50)
IPI at screening, n (%)			
0	1 (17)	0	1 (8)
1	1 (17)	1 (17)	2 (17)
2	1 (17)	1 (17)	2 (17)
3	3 (50)	2 (33)	5 (42)
4	0	2 (33)	2 (17)
CD20+/CD19+ at screening, n (%)			
Yes	6 (100)/6 (100)	6 (100)/4 (67)	12 (100)/10 (83)

CD, cluster of differentiation; DLBCL, diffuse large B cell lymphoma; IPI, International Prognostic Index; MCL, mantle cell lymphoma; NOS, not other specified; PMBCL, primary mediastinal B cell lymphoma; TFL, transformed follicular lymphoma

Results

MB-CART2019.1 manufacturing

- A non-mobilized leukapheresis was collected from 12 patients. The leukapheresis was not cryopreserved before shipment to the manufacturing site
- Manufacturing of MB-CART2019.1 was completed for all 12 enrolled patients within 12 days
- The final drug product was not cryopreserved when shipped to the clinical site
- The mean time of infusion from leukapheresis was 14 days (**Figure 2**)

Safety and toxicity

DLTs and AEs of special interest are shown in **Table 2** and **Figure 3**

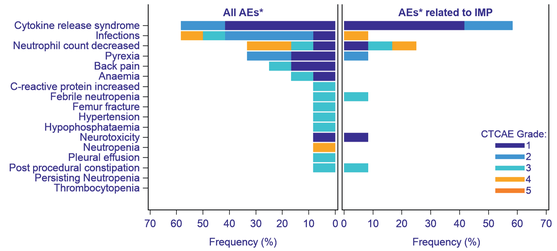
- No DLTs were observed
- No patients experienced cytokine release syndrome (CRS) or neurotoxicity ≥Grade 3
- Hematotoxicity was limited, with no anemia or thrombocytopenia ≥Grade 3 beyond Day 28. Only two patients experienced intermittent neutropenia ≥Grade 3 beyond Week 8 following treatment

Table 2. Dose-limiting toxicities and adverse events of special interest

Treatment-emergent adverse event	Dose level 1 (N=6) Patients, n (%)	Dose level 2 (N=6) Patients, n (%)	Total (N=12) Patients, n (%)
DLTs	**0**	**0**	**0**
CRS			
Any grade	3 (50)	4 (67)	7 (58)
Grade ≥3	0	0	0
Neurotoxicity			
Any grade	0	1 (17)	1 (8)
Grade ≥3	0	0	0
Infections and infestations			
Any grade	4 (67)	3 (50)	7 (58)
Grade ≥3	2 (33)	0	2 (17)
Use of tocilizumab (AE resolved)	0	1 (17)	1 (8)

AE, adverse event; CRS, cytokine release syndrome; DLT, dose-limiting toxicity

Figure 3. Adverse events of special interest

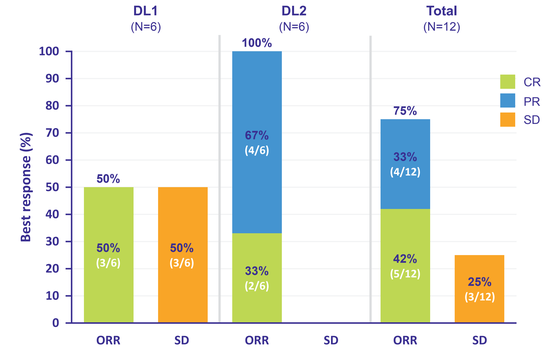


*Only AEs with a start date on or after date of leukapheresis were considered. Patients from DL1 and DL2 were considered (N=12)
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events (v5) (events were coded according to MedDRA Version 23.0); DL, dose level; IMP, investigational medicinal product

Efficacy: Objective response rate

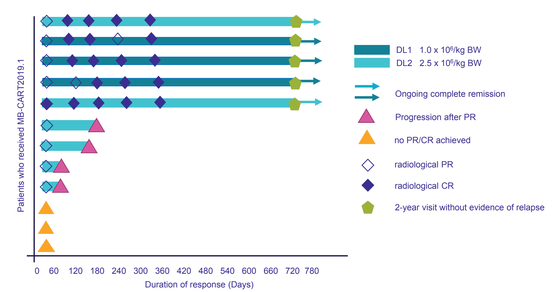
- Response assessment was performed at Week 4, Month 9, and Month 12 via computerized tomography (CT) and at Week 12 and Month 6 via positron emission tomography-CT (PET-CT) using the Lugano classification[7]
- The best ORR per DL is shown in **Figure 4**
  - The total best ORR for both DLs combined was 75% (3/6 patients in DL1 and 6/6 patients in DL2)
  - A total of 5/12 patients (3/6 in DL1 and 2/6 in DL2) achieved a complete response (CR).[a] Among those 5 patients, all had ongoing CR[b] at 12 months and all completed a 2-year follow-up visit without evidence of relapse as per investigator assessment (**Figure 5**)
  - Patients with a partial response or stable disease as best objective response ultimately progressed

Figure 4. Best objective response rate (investigator assessment)*



*One patient with PR in DL2 did not receive fludarabine during lymphodepletion
CR, complete response; DL, dose level; ORR, objective response rate; PR, partial response; SD, stable disease

Figure 5. Duration of response (investigator assessment)

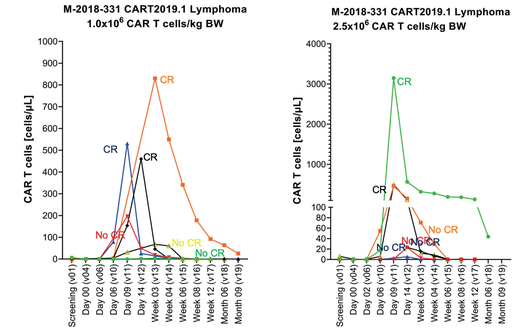


BW, body weight; CR, complete response; DL, dose level; PR, partial response

Persistence of CAR T cells, CAR T cell expansion, and clinical response

- In this analysis, patients were grouped according to best objective response (CR *vs.* non-CR). Irrespective of the DL, all patients with CR had a C_{max} ≥460 cells/µL (C_{max}: 1,092.5 cells/µL; range 460.1–3,147.0 cells/µL) (**Figure 6**)
- Patients without a CR had a mean C_{max} of 111.0 cells/µL (range 3.9–458.0 cells/µL)
- Mean $AUC_{d0\text{-}d28}$ for patients with a CR was 7,901 d*cells/µL (range 2,399.2–19,574.7 d*cells/µL) *versus* a mean $AUC_{d0\text{-}d28}$ of 942.0 d*cells/µL (range 39.3–3,471.62 d*cells/µL) in patients without a CR
- Mean time of CAR T cell persistence in patients with a CR was 491 days (range 274–736 days)
- All 5 patients with a CR had detectable CAR T cells beyond Month 6

Figure 6. CAR T cell expansion and clinical response (CR *vs.* non-CR)



BW, body weight; CAR, chimeric antigen receptor; CR, complete response

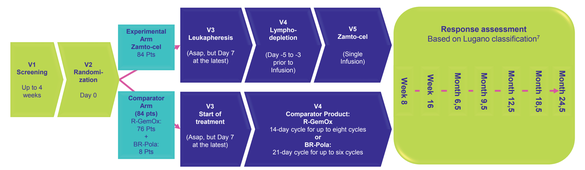
Conclusions

- MB-CART2019.1 was infused in 100% of enrolled patients
- Both DLs of MB-CART2019.1 were well tolerated in this Phase I/II trial with no DLT observed
- No CRS or neurotoxicity ≥Grade 3 were observed in any DL
- The recommended dose of MB-CART2019.1 is 2.5 × 10^6 CAR T cells/kg BW
- All 5 patients with a PET-negative CR had high peak CAR T cell expansion and have completed the 2-year follow-up visit without evidence of relapse or the need for new anti-lymphoma therapy

Future directions for research

- MB-CART2019.1 is currently being evaluated in a randomized, multicenter, open-label Phase II trial to evaluate the efficacy and safety of MB-CART2019.1 compared with standard of care (SoC) therapy in participants with r/r DLBCL who are not eligible for high-dose chemotherapy and autologous stem-cell transplantation **(DALY 2-EU trial)** (NCT04844866) **(Figure 7)**
- This study should determine superiority of MB-CART2019.1 treatment compared with SoC therapy using R-GemOx (rituximab, gemcitabine, and oxaliplatin) with respect to progression-free survival in second-line therapy
- The **DALY 2-EU trial** has been active in Europe since August 2021 and planned with more than 45 investigational sites in more than 10 European countries

Figure 7. Schematic overview of European Phase II MB-CART2019.1 trial



Asap, as soon as possible; BR-Pola, bendamustine, rituximab-polatuzumab vedotin; Pts, patients; R-GemOx, rituximab, gemcitabine, and oxaliplatin; V, visit; Zamto-cel, zamtocabtagene autoleucel

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Footnotes and abbreviations: [a]As radiologically documented by a negative PET-CT scan; [b]as radiologically documented by a PET-CT or CT scan
AE, adverse event; AUC, area under the curve; B-NHL, B cell non-Hodgkin lymphoma; BW, body weight; CAR, chimeric antigen receptor; CD, cluster of differentiation; C_{max}, maximum concentration; CR, complete response; CRS, cytokine release syndrome; CT, computerized tomography; DL, dose level; DLBCL, diffuse large B cell lymphoma; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; ORR, objective response rate; PET, positron emission tomography; r/r, relapsed/refractory; R-GemOx, rituximab, gemcitabine, and oxaliplatin; SoC, standard of care