Poster #PF1152

Mi Kwon, MD, PhD | mi.kwon@salud.madrid.org

Rapcabtagene Autoleucel (YTB323) in Patients with Relapsed/Refractory Diffuse Large B-cell Lymphoma: A Phase II Trial Clinical Update

Mi Kwon[1]; Peter A. Riedell[2]; Ian W. Flinn[3]; Michael J. Dickinson[4]; Carlos Solano[5], Ulrich Jaeger[6]; Javier Briones-Meijide[7]; Koji Kato[8]; Shaun Flemming[9]; Emmanuel Bachy[10]; Alessandro Rambaldi[11]; Leyla O. Shune[12]; Nirav N. Shah[13]; Didier Blaise[14]; Matthew J. Frigault[15]; Aravind Ramakrishnan[16]; Anne Yang[17]; David Pearson[18]; Aiesha Zia[19]; Eduardo Segura[20]; Aisha Masood[17]; Pere Barba[21]

[1]Department of Hematology, Hospital General Universitario Gregorio Marañón, Institute of Health Research Gregorio Marañón, Madrid, Spain; [2]David and Etta Jonas Center for Cellular Therapy, University of Chicago, Chicago, Illinois, United States of America; [3]Tennessee Oncology-OneOncology, Nashville, Tennessee, United States of America; [4]Peter MacCallum Cancer Centre and Royal Melbourne Hospital and the University of Melbourne, Melbourne, Victoria, Australia; [5]Department of Hematology, Hospital Clínico Universitario, University of Valencia, Valencia, Spain; [6]Clinical Division of Hematology and Hemostaseology, Department of Medicine I, Vienna General Hospital – Medical University of Vienna, Vienna, Austria; [7]Hematology Department, Hospital Santa Creu i Sant Pau, Barcelona, Spain; [8]Department of Hematology, Oncology, and Cardiovascular Medicine, Kyushu University Hospital, Fukuoka Prefecture, Japan; [9]Department of Haematology, Alfred Hospital, Melbourne, Victoria, Australia; [10]Hospices Civils de Lyon and Université Claude Bernard Lyon 1, Lyon, France; [11]Department of Oncology and Hematology, University of Milan and Azienda Socio-Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy; [12]University of Kansas Medical Center, Kansas City, Kanas, United States of America; [13]Medical College of Wisconsin, Milwaukee, Wisconsin, United States of America; [14]Département d'Hématologie, Programme de Transplantation et de Thérapie Cellulaire, Centre de Recherche en Cancérologie de Marseille, Aix-Marseille University, Institut Paoli Calmettes, Marseille, France; [15]Massachusetts General Hospital, Boston, Massachusetts, United States of America; [16]Department of Hematology, St David's South Austin Medical Center, Austin, Texas, United States of America; [17]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, United States of America; [18]Novartis Institutes for BioMedical Research, Basel, Switzerland; [19]Novartis Pharma AG, Basel, Switzerland; [20]Novartis Pharmaceuticals Corporation, Madrid, Spain; [21]Hematology Department, Hospital Universitari Vall d'Hebrón, Universitat Autònoma de Barcelona, Barcelona, Spain.

KEY FINDINGS & CONCLUSIONS

- At the 12.5×10^6 cell dose, rapcabtagene autoleucel achieved high response rates (ORR, 88%; CRR, 65%)
  - Median follow-up was 16 months
- Rapcabtagene autoleucel responses were durable
  - 12-month DOR probability was 54% for all responders and 69% for patients with a BOR of CR
  - 12-month PFS probability was 48% for all patients and 79% for patients with a CR at month 3
- Rapcabtagene autoleucel has a favorable safety profile
  - Low rates of grade ≥3 CRS (6%) and ICANS (5%) were reported in the overall patient population
- Risk-benefit analyses support use of the lower-dose LD regimen before infusion

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INTRODUCTION

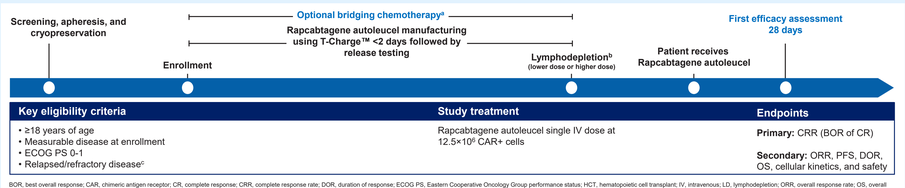
- Rapcabtagene autoleucel is a next-generation CD19-directed chimeric antigen receptor (CAR) T-cell (CAR-T) therapy that utilizes the T-Charge™ platform to preserve T-cell stemness by rapidly manufacturing product (<2 days)[1]
- The phase 1 study identified the 12.5×10^6 CAR+ viable T-cell dose for further investigation in the treatment of patients with relapsed/refractory (r/r) diffuse large B-cell lymphoma (DLBCL)[2]
- Here we report an interim descriptive analysis of the ongoing phase 2 clinical trial (NCT03960840)[3] with a median follow-up of 16 months (N = 63; data cutoff, February 1, 2024)

METHODS

Study design

- Study design, including eligibility criteria and key endpoints, can be found in **Figure 1**
- Eligible patients received a single dose of rapcabtagene autoleucel (12.5 × 10^6 CAR+ viable T cells)
- Bridging therapy before infusion was permitted
- Primary endpoint was complete response rate (CRR; best overall response [BOR] of complete response [CR]).
- Secondary endpoints included overall response rate (ORR), progression-free survival (PFS), duration of response (DOR), cellular kinetics, and safety
- Cellular kinetics were determined by measurement of transgene levels by quantitative polymerase chain reaction

Figure 1. Study Design



BOR, best overall response; CAR, chimeric antigen receptor; CR, complete response; CRR, complete response rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HCT, hematopoietic cell transplant; IV, intravenous; LD, lymphodepletion; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.
[a]Optional bridging therapies were investigator's decision. [b]Two LD regimens were assessed as a part of this phase 2 trial. Lower-dose LD was defined as fludarabine/cyclophosphamide 25/250 mg/m^2 for 3 days. Higher-dose LD was defined as fludarabine/cyclophosphamide 30/500 mg/m^2 for 3 days. [c]Relapsed/refractory disease is defined as patients who have failed two or more lines of chemotherapy and either progressed (or relapsed) after autologous HCT or were ineligible for or did not consent to the procedure.

RESULTS

Baseline Characteristics

- As of February 1, 2024, 63 patients had received rapcabtagene autoleucel with a median follow-up of 16.4 months (range: 0.1-44.1; **Table 1**)
- Twenty-eight patients (44.4%) received lower-dose lymphodepletion (LD; fludarabine/cyclophosphamide: 25/250 mg/m^2 for 3 days) with a median follow-up 32.8 months, and 33 patients (52.4%) received higher-dose LD (fludarabine/cyclophosphamide: 30/500 mg/m^2 for 3 days) with a median follow-up of 5.4 months.
- Two patients (3.2%) received bendamustine (90 mg/m^2) LD

Table 1. Key Patient and Baseline Disease Characteristics

Baseline variable	Infused set (N = 63)[a]
Median age, years (range)	64 (26-81)
≥65 years, n (%)	29 (46.0)
IPI score, n (%)	
<3	34 (54.0)
≥3	24 (38.1)
Unknown	5 (7.9)
Rearrangements in *MYC/BCL2/BCL6* genes, n (%)	
Double/triple hits	16 (25.4)
Negative	25 (39.7)
Unknown	22 (34.9)
Relapsed/refractory disease status, n (%)	
Refractory to last line of therapy	37 (58.7)
Refractory to all prior lines	13 (20.6)
Relapsed after last line of therapy	26 (41.3)
Histology, n (%)	
DLBCL	52 (82.5)
Transformed lymphoma	8 (12.7)
Elevated LDH (>ULN), n (%)	27 (42.9)
Prior HCT, n (%)	19 (30.2)
Prior lines of therapy, n (%)	
2	46 (73.0)
≥3	17 (27.0)
Received bridging therapy, n (%)	38 (60.3)

DLBCL, diffuse large B-cell lymphoma; HCT, hematopoietic cell transplant; IPI, International Prognostic Index; LDH, lactate dehydrogenase; ULN, upper limit of normal. [a]Two patients were pending infusion as of data cutoff. One patient died prior to infusion of intestinal obstruction related to the study indication.

Efficacy

Response Rates

- Among 60 infused patients with r/r DLBCL who had ≥1 month follow-up, ORR was 88.3% and CRR was 65%. CRR at 3, 6, and 12 months were 54.5% (30/55), 56.8% (25/44), and 47.4% (18/38), respectively (**Table 2**)
- High CR rates at 3 months were observed across most patient subgroups, including high-risk populations: 89% for those with prior hematopoietic cell transplant, 70% for those relapsed after last line of therapy, 64% for those aged ≥65 years, 53% for those with ≥3 prior therapies, 46% for those with an International Prognostic Index ≥3, 46% for those refractory to all prior lines of therapy, and 44% for those refractory to the last line of therapy. A lower CR rate of 29% was reported for patients with elevated lactate dehydrogenase before infusion

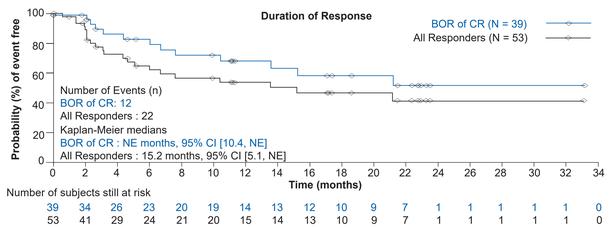
Table 2. Best Overall Response Rate

Baseline variable	Infused set (N = 63)[a]
Median follow-up, months (range)	16.4 (0.1-44.1)
Overall response rate,[b] n (%) [95% CI][c]	**53 (88.3) [77.4-95.2]**
Best overall response	
CR, n (%) [95% CI]	**39 (65.0) [51.6-76.9]**
CR excluding patients with CR before infusion, n/N (%)[d]	**35/56 (62.5)**
PR, n (%)	14 (23.3)
Complete response rate, n/N (%)	
Month 3	30/55[e] (54.5)
Month 6	25/44[e] (56.8)
Month 12	18/38[e] (47.4)

BOR, best overall response; CR, complete response; PD, progressive disease; PR, partial response.
[a]Patients infused at least 28 days before cutoff. [b]Overall response rate = CR + PR. [c]95% CIs are exact Clopper-Pearson CIs. [d]Excludes patients who were in CR prior to receiving rapcabtagene autoleucel due to either a late effect of prior therapies or bridging chemotherapy. [e]Patients infused at least 3, 6, or 12 months prior to data cutoff and have a month 3, 6, or 12 assessment, or, discontinued due to PD/death/new therapy prior to their month 3, 6, or 12 assessment.

DOR

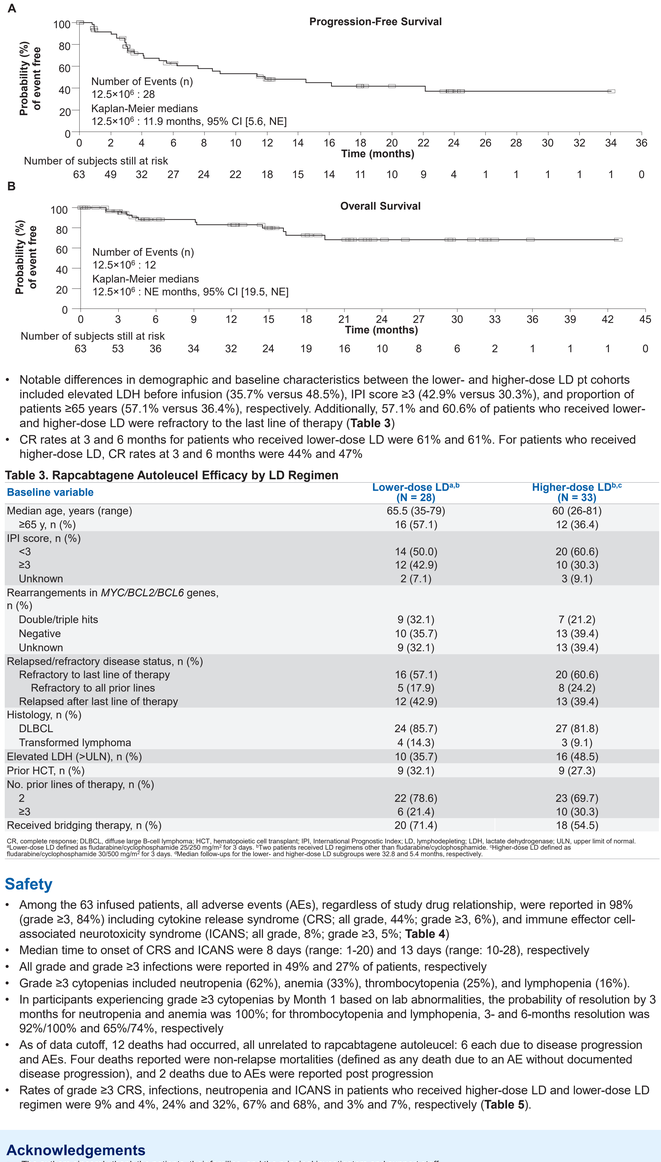
- Median DOR was 15.2 months (5.1-not estimable [NE]) in all responding patients (N = 53). In patients with a BOR of CR (N = 39), the median DOR was not estimable (10.4-NE) and the 12-month DOR was 69% (**Figure 2**)



BOR, best overall response; CR, complete response; DOR, duration of response; NE, not estimable; PD, progressive disease; PR, partial response

PFS and OS

- Median PFS was 11.9 months in all patients. Among patients in CR at 3 months, the median PFS was not reached. The PFS rates at 12 months were 48.2% for all patients and 79.3% for patients in CR at 3 months (**Figure 3A**)
- For both all patients and those in CR at 3 months, the median OS was not reached. The OS rates at 12 months were 83% for all patients and 100% for patients in CR at 3 months (**Figure 3B**)



- Notable differences in demographic and baseline characteristics between the lower- and higher-dose LD pt cohorts included elevated LDH before infusion (35.7% versus 48.5%), IPI score ≥3 (42.9% versus 30.3%), and proportion of patients ≥65 years (57.1% versus 36.4%), respectively. Additionally, 57.1% and 60.6% of patients who received lower- and higher-dose LD were refractory to the last line of therapy (**Table 3**)
- CR rates at 3 and 6 months for patients who received lower-dose LD were 61% and 61%. For patients who received higher-dose LD, CR rates at 3 and 6 months were 44% and 47%

Table 3. Rapcabtagene Autoleucel Efficacy by LD Regimen

Baseline variable	Lower-dose LD[a,b] (N = 28)	Higher-dose LD[b,c] (N = 33)
Median age, years (range)	65.5 (35-79)	60 (26-81)
≥65 y, n (%)	16 (57.1)	12 (36.4)
IPI score, n (%)		
<3	14 (50.0)	20 (60.6)
≥3	12 (42.9)	10 (30.3)
Unknown	2 (7.1)	3 (9.1)
Rearrangements in *MYC/BCL2/BCL6* genes, n (%)		
Double/triple hits	9 (32.1)	7 (21.2)
Negative	10 (35.7)	13 (39.4)
Unknown	9 (32.1)	13 (39.4)
Relapsed/refractory disease status, n (%)		
Refractory to last line of therapy	16 (57.1)	20 (60.6)
Refractory to all prior lines	5 (17.9)	8 (24.2)
Relapsed after last line of therapy	12 (42.9)	13 (39.4)
Histology, n (%)		
DLBCL	24 (85.7)	27 (81.8)
Transformed lymphoma	4 (14.3)	3 (9.1)
Elevated LDH (>ULN), n (%)	10 (35.7)	16 (48.5)
Prior HCT, n (%)	9 (32.1)	9 (27.3)
No. prior lines of therapy, n (%)		
2	22 (78.6)	23 (69.7)
≥3	6 (21.4)	10 (30.3)
Received bridging therapy, n (%)	20 (71.4)	18 (54.5)

CR, complete response; DLBCL, diffuse large B-cell lymphoma; HCT, hematopoietic cell transplant; IPI, International Prognostic Index; LD, lymphodepleting; LDH, lactate dehydrogenase; ULN, upper limit of normal. [a]Lower-dose LD defined as fludarabine/cyclophosphamide 25/250 mg/m^2 for 3 days. [b]Two patients received LD regimens other than fludarabine/cyclophosphamide. [c]Higher-dose LD defined as fludarabine/cyclophosphamide 30/500 mg/m^2 for 3 days. [d]Median follow-ups for the lower- and higher-dose LD subgroups were 32.8 and 5.4 months, respectively.

Safety

- Among the 63 infused patients, all adverse events (AEs), regardless of study drug relationship, were reported in 98% (grade ≥3, 84%) including cytokine release syndrome (CRS; all grade, 44%; grade ≥3, 6%), and immune effector cell-associated neurotoxicity syndrome (ICANS; all grade, 8%; grade ≥3, 5%; **Table 4**)
- Median time to onset of CRS and ICANS were 8 days (range: 1-20) and 13 days (range: 10-28), respectively
- All grade and grade ≥3 infections were reported in 49% and 27% of patients, respectively
- Grade ≥3 cytopenias included neutropenia (62%), anemia (33%), thrombocytopenia (25%), and lymphopenia (16%).
- In participants experiencing grade ≥3 cytopenias by Month 1 based on lab abnormalities, the probability of resolution by 3 months for neutropenia and anemia was 100%; for thrombocytopenia and lymphopenia, 3- and 6-months resolution was 92%/100% and 65%/74%, respectively
- As of data cutoff, 12 deaths had occurred, all unrelated to rapcabtagene autoleucel: 6 each due to disease progression and AEs. Four deaths reported were non-relapse mortalities (defined as any death due to an AE without documented disease progression), and 2 deaths due to AEs were reported post progression
- Rates of grade ≥3 CRS, infections, neutropenia and ICANS in patients who received higher-dose LD and lower-dose LD regimen were 9% and 4%, 24% and 32%, 67% and 68%, and 3% and 7%, respectively (**Table 5**).

Table 4. CRS and ICANS after Rapcabtagene autoleucel infusion

	Rapcabtagene autoleucel 12.5×10^6 (N = 63)
CRS,[a] n (%)	**28 (44.4)**
Grade 1	17 (27.0)
Grade 2	7 (11)
Grade 3	2 (3.2)
Grade 4	2 (3.2)
Median time to onset, days (range)	8 (1-20)
Grade 3/4[a]	7.5 (7-11)
Median time from onset to resolution, days (range)	6 (1-25)
Admitted to ICU for CRS, n/N (%[b])	6/28 (21.4)
Management of CRS, n/N (%[b])	
Tocilizumab	15/28 (53.6)
Corticosteroids	7/28 (25.0)
ICANS, n (%)	**5 (7.9)**
Grade 1	2 (3.2)
Grade 2	0
Grade 3	2 (3.2)
Grade 4	1 (1.6)
Median time to onset, days (range)	13 (10-28)
Grade 3/4	18.5 (13-24)
Median time from onset to resolution, days (range)	17 (11-24)
Management of ICANS, n/N (%[c])	
Dexamethasone	4/5 (80.0)
Methylprednisolone	2/5 (40.0)
Anakinra	2/5 (40.0)

ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; ICU, intensive care unit. [a]Based on ASTCT grading (per Lee 2019)[4]. [b]Percentage calculated based on the number of patients with CRS. [c]Percentage calculated based on the number of patients with ICANS

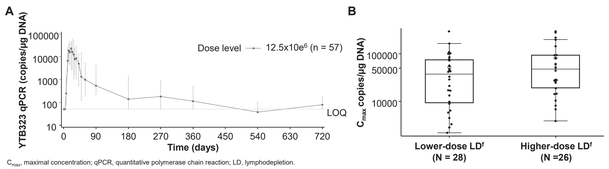
Table 5. Rapcabtagene Autoleucel Safety Profile by LD Regimen

	Lower-dose LD[a,b] (N = 28)	Higher-dose LD[b,c] (N = 33)
Median follow-up, months (range)	32.8 (21.3-44.1)	5.4 (0.1-23.4)
Adverse events, n (%)[d]		
Any grade	28 (100)	32 (97.0)
Grade ≥3	27 (96.4)	25 (75.8)
Deaths, n (%)	10 (35.7)	2 (6.1)
Infections, n (%)		
Any grade	14 (50.0)	16 (48.5)
Grade ≥3	9 (32.1)	8 (24.2)
Cytopenias, n (%)		
Anemia	17 (60.7)	14 (42.4)
Leukopenia	0	3 (9.1)
Lymphopenia	7 (25.0)	4 (12.1)
Neutropenia	19 (67.9)	22 (66.7)
Thrombocytopenia	11 (39.3)	9 (27.3)
CRS,[e] n (%)		
Any grade	11 (39.3)	16 (48.5)
Grade 3/4	1 (3.6)	3 (9.1)
ICANS, n (%)		
Any grade	4 (14.3)	1 (3.0)
Grade 3/4	2 (7.1)	1 (3.0)

AE, adverse event; ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; LD, lymphodepletion.
[a]Lower-dose LD defined as fludarabine/cyclophosphamide 25/250 mg/m^2 for 3 days. [b]Two patients received LD regimens other than fludarabine/cyclophosphamide. [c]Higher-dose LD defined as fludarabine/cyclophosphamide 30/500 mg/m^2 for 3 days. [d]All AEs reported regardless of study drug relationship. [e]Based on ASTCT grading (per Lee 2019)[4]

Cellular Kinetics

- Rapcabtagene autoleucel showed high cellular expansion with extended persistence and B-cell aplasia (**Figure 4A**). Comparable cellular expansion was seen at both LD dose regimens (**Figure 4B and Table 6**)
- Predicted fludarabine and cyclophosphamide exposure (AUC^0) did not correlate with cellular expansion (C_{max}), rates of AEs (CRS, infections), or CRR (BOR, month 3, month 6, month 12)



C_{max}, maximal concentration; qPCR, quantitative polymerase chain reaction; LD, lymphodepletion.

Table 6. Rapcabtagene Autoleucel Cellular Kinetics

	Rapcabtagene autoleucel 12.5×10^6 (N = 63)
Median C_{max}, copies/µg DNA	41,800
Higher-dose LD[a,b]	47,100
Lower-dose LD[b,c]	36,900
Median duration of persistence in peripheral blood,[d] months (95% CI)	16.4 (6.3-NR)
12-month persistence probability, % (95% CI)	62.8 (40.9-78.5)
Median duration of B-cell aplasia,[e] months (95% CI)	NR (17.7-NR)
12-month B-cell aplasia probability, % (95% CI)	88.7 (67.7-96.4)

AUC, area under the curve; BOR, best overall response; CRS, cytokine release syndrome; C_{max}, maximal concentration; eGFR, estimated glomerular filtration rate; LD, lymphodepleting; LOQ, limit of quantification; NR, not reached; PK, pharmacokinetics; qPCR, quantitative polymerase chain reaction.
[a]Lower-dose LD defined as fludarabine/cyclophosphamide 25/250 mg/m^2 for 3 days. [b]Two patients received LD regimens other than fludarabine/cyclophosphamide. [c]Higher-dose LD defined as fludarabine/cyclophosphamide 30/500 mg/m^2 for 3 days. [d]Persistence defined as time to nonquantifiable transgene by qPCR based on Kaplan-Meier analysis. [e]40 5 patients with B-cell recovery and evaluable PD data showed nonquantifiable transgene 28 to 302 days before B-cell recovery. [f]The diamond represents the mean. Lower and upper whiskers extend to most extreme points within 1.5*IQR of Q1 and Q3, respectively. [g]AUC predicted based on patient covariates (weight, eGFR) using a published population PK model.

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