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YTB323 (Rapcabtagene Autoleucel) Demonstrates Durable Efficacy and a Manageable Safety Profile in Patients with Relapsed/Refractory Diffuse Large B-Cell Lymphoma (r/r DLBCL): Phase I Study Update

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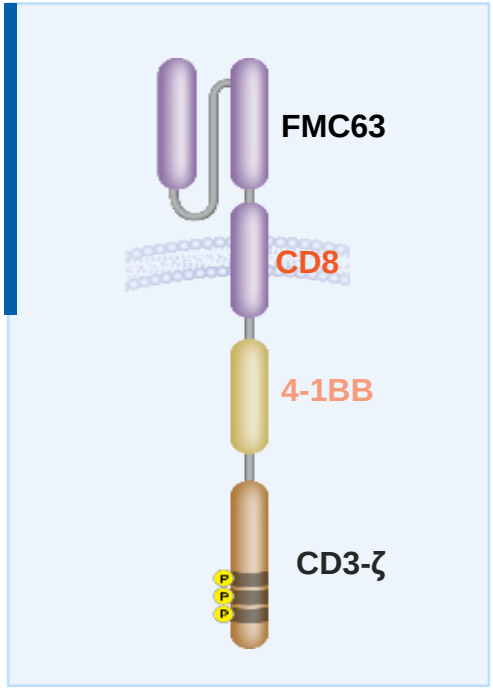
Introduction

- Despite novel treatment options, a substantial proportion of patients with r/r DLBCL do not achieve sustained remission[1,2] or do not have timely access to these therapies
  - ➢ There remains an unmet need to further improve response rates, durability, and accessibility to patients
- Rapcabtagene autoleucel (YTB323) is an autologous CD19-directed CAR-T cell therapy rapidly manufactured (<2 days) using the next-generation T-Charge™ platform that preserves T-cell stemness
- **This presentation focuses on the r/r DLBCL cohort (N=47) with 13 months' median follow-up (data cutoff September 15, 2022) in the Phase I, first-in-human trial[3] of rapcabtagene autoleucel**



CAR, chimeric antigen receptor; CD, cluster of differentiation; DLBCL, diffuse large B-cell lymphoma; r/r, relapsed or refractory.

1. Friedberg JW. *Hematology Am Soc Hematol Educ Program*. 2011;2011:498-505; 2. Crump M, et al. Blood. 2017;130(16):1800-1808; 3. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03960840. Accessed October 26, 2022.

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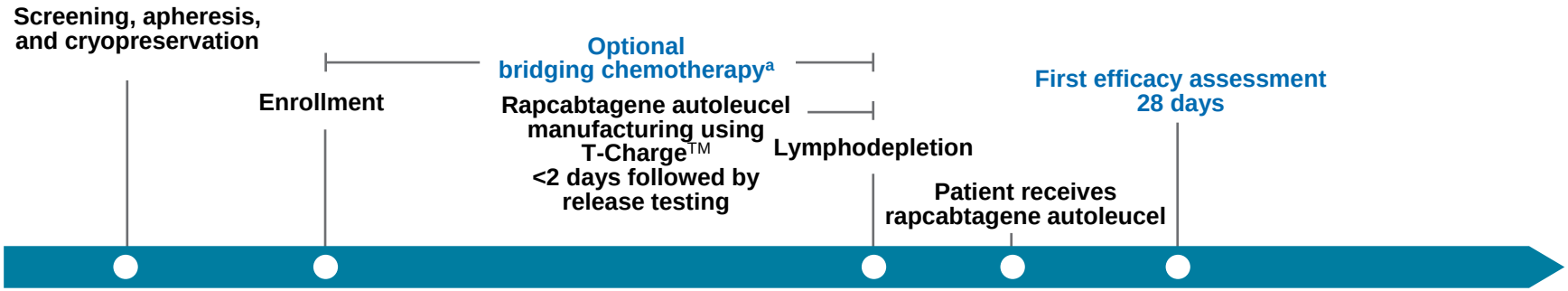
Study Design: DLBCL Treatment Arm



Key eligibility criteria	Study treatment	End points
• ≥18 years of age • Measurable disease at enrollment • ECOG PS 0-1 • Relapsed/refractory disease[b]	• Lymphodepleting chemotherapy: fludarabine (30 mg/m^2 IV daily ×3 days) + cyclophosphamide (500 mg/m^2 IV daily ×3 days) • Rapcabtagene autoleucel dose levels (single IV dose): − DL1, 2.5×10^6 CAR+ cells − DL2, 12.5×10^6 CAR+ cells − DL3, 25×10^6 CAR+ cells − DL4, 40×10^6 CAR+ cells	**Primary:** Incidence of DLTs[c] and safety to determine a recommended dose **Secondary:** Cellular kinetics, ORR, DOR, OS

CAR, chimeric antigen receptor; DL, dose level; DLBCL, diffuse large B-cell lymphoma; DLT, dose-limiting toxicity; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HSCT, hematopoietic stem cell transplant; IV, intravenous; ORR, overall response rate; OS, overall survival.
[a]Optional bridging therapies were investigator's decision. [b]Relapsed/refractory disease is defined as patients who have failed 2 or more lines of chemotherapy and either progressed (or relapsed) after autologous HSCT or were ineligible for or did not consent to the procedure. [c]Within 28 days of receiving rapcabtagene autoleucel.

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Patient and Disease Baseline Characteristics

Baseline Variable	Rapcabtagene Autoleucel Infused (N=47)
Median age (range), y	65 (35-79)
IPI score, n (%)	
<3	25 (53.2)
≥3	20 (42.6)
Unknown	2 (4.3)
Rearrangements in *MYC/BCL2/BCL6* genes, n (%)	
Double/triple hits	16 (34.0)
Negative	14 (29.8)
Unknown	17 (36.2)
Relapsed/refractory disease status, n (%)	
Refractory to all prior lines	10 (21.3)
Refractory to last line of therapy only	16 (34.0)
Relapsed after last line of therapy	21 (44.7)
Histology, n (%)	
DLBCL	45 (95.7)
Transformed lymphoma/other	2 (4.3)
Elevated LDH (>ULN),[a] n (%)	26 (55.3)
Prior HSCT, n (%)	14 (29.8)
No. prior lines of therapy, n (%)	
2	34 (72.3)
≥3	13 (27.7)
Time since most recent relapse/progression to rapcabtagene autoleucel infusion, median (range), mo	2.8 (1.4-11.1)
Received bridging therapy,[b] n (%)	32 (68.1)

DLBCL, diffuse large B-cell lymphoma; HSCT, hematopoietic stem cell transplant; IPI, International Prognostic Index; LD, lymphodepleting; LDH, lactate dehydrogenase; ULN, upper limit of normal.
[a]Varies depending on the upper limit of normal for each site. [b]Bridging was defined as the time after leukapheresis to the start of LD chemotherapy.

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Rapcabtagene Autoleucel: Best Overall Response

	Rapcabtagene Autoleucel Dose Levels			
	DL1 2.5×10^6 (N=4)	DL2 12.5×10^6 (N=30)	DL3 25×10^6 (N=7)	DL4 40×10^6 (N=6)
	n (%)	n (%)	n (%)	n (%)
Best overall response				
CR	3 (75)	**22 (73)**	5 (71)	4 (67)
CR excluding patients with CR before infusion[a]	1/2 (50)	**19/27 (70)**	5/7 (71)	4/6 (67)
PR	0	**3 (10)**	0	0
Overall response rate[b] [95% CI][c]	3 (75) [19.4-99.4]	**25 (83) [65.3-94.4]**	5 (71) [29.0-96.3]	4 (67) [22.3-95.7]

- Median follow-up (infusion to cutoff date) across the 4 dose levels was 13 months (4.4-34.3 months)

CR, complete response; DL, dose level; PR, partial response.
Patients infused at least 28 days before cutoff.
[a]Excludes patients who were in CR prior to receiving rapcabtagene autoleucel due to either a late effect of prior therapies or bridging chemotherapy.
[b]Overall response rate = CR + PR.
[c]95% CIs are exact Clopper-Pearson CIs.

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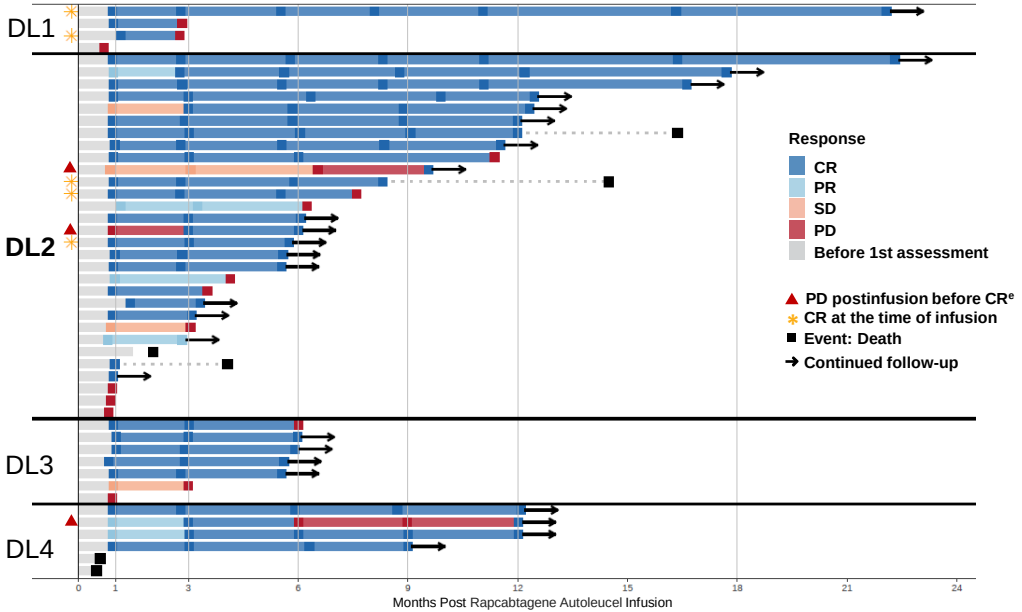
Rapcabtagene Autoleucel Responses Appear Durable

	DL2 12.5×10^6 (N=30)
Median follow-up (range)	16 mo (4.4-27.5)
BOR of CR	22/30 (**73%**)
CR at 3 mo	18/30[a] (**60%**)
CR at 6 mo	16/26[b] (**62%**)
CR at 9 mo	8/19[c] (**42%**)
CR at 12 mo	8/16[d] (**50%**)
Median DOR (95% CI)	**16 mo** (10.4-NE)



BOR, best overall response; CR, complete response; DL, dose level; DOR, duration of response; HSCT, hematopoietic stem cell transplant; NE, not estimable; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Patients infused ≥3 months before cutoff. [b]Patients infused ≥6 months before cutoff. [c]Patients infused ≥9 months before cutoff. [d]Patients infused ≥12 months before cutoff. [e]Patients experienced PD after rapcabtagene autoleucel infusion and then later, without receiving any further antilymphoma therapy, achieved CR.
Six deaths were due to disease progression (1 at DL1, 3 at DL2, 1 at DL3, and 1 at DL4), 2 deaths were due to COVID or COVID-related pneumonia (at DL2), 1 was due to intestinal hemorrhage (at DL2), 1 was due to acute respiratory failure (at DL2), 1 was due to tumor lysis syndrome (at DL2), 1 was due to septic shock (at DL4), 1 was due to sepsis (at DL1), and 1 was due to an unknown reason (at DL2).

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Rapcabtagene Autoleucel Has a Manageable Safety Profile

AEs,[a] n (%)	Treated Patients (N=47)			
	DL1 2.5×10^6 (N=4)	DL2 12.5×10^6 (N=30)	DL3 25×10^6 (N=7)	DL4 40×10^6 (N=6)
Any AE				
Any grade	4 (100)	**30 (100)**	7 (100)	6 (100)
Grade ≥3	4 (100)	**28 (93)**	7 (100)	6 (100)
Dose-limiting toxicities	0	**2 (7)[b]**	0	0
Death[c]	2 (50)	**9 (30)**	1 (14)	2 (33)
Related to rapcabtagene autoleucel	0	**0**	0	0
Infections				
Any grade	3 (75)	**9 (30)**	4 (57)	3 (50)
Grade ≥3	1 (25)	**5 (17)**	1 (14)	2 (33)

AE, adverse event; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; DL, dose level; DLT, dose-limiting toxicity; MedDRA, Medical Dictionary for Regulatory Activities. MedDRA version 25.0 and CTCAE version 5.0 have been used for the reporting of AEs.
[a]All AEs reported regardless of study drug relationship. [b]DLTs were grade 4 CRS per Lee 2014 criteria and grade 4 pancytopenia lasting >28 days post rapcabtagene autoleucel infusion. [c]Six deaths were due to disease progression (1 at DL1, 3 at DL2, 1 at DL3, and 1 at DL4), 2 deaths were due to COVID or COVID-related pneumonia (at DL2), 1 was due to intestinal hemorrhage (at DL2), 1 was due to acute respiratory failure (at DL2), 1 was due to tumor lysis syndrome (at DL2), 1 was due to septic shock (at DL4), 1 was due to sepsis (at DL1), and 1 was due to an unknown reason (at DL2).

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CRS Was Low Grade and Resolved Within a Median of 6 Days from Onset at DL2

	Treated Patients (N=47)			
	DL1 2.5×10^6 (N=4)	DL2 12.5×10^6 (N=30)	DL3 25×10^6 (N=7)	DL4 40×10^6 (N=6)
CRS,[a] n (%)	1 (25)	**11 (37)**	2 (29)	2 (33)
Grade 1/2	1 (25)	**9 (30)**	2 (29)	2 (33)
Grade 3/4	0	**2 (7)**	0	0
Time to onset, days	9	**8 (1-17)[b]**	7, 36	2, 9
Time from onset to resolution, days	5	**6 (2-25)[b]**	5, 10	5, 7
Admitted to ICU for CRS, n/N (%)	0	**3/11 (27)**	0	0
Management of CRS, n/N (%[c])				
Tocilizumab	0	**8/11 (73)**	1/2 (50)	0
Corticosteroids	0	**4/11 (36)**	0	0
Vasopressors	0	**2/11 (18)**	0	0

ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; DL, dose level; ICU, intensive care unit.
[a]Per ASTCT 2019 criteria. [b]Median (range). [c]Percentage calculated based on the number of patients with CRS.

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ICANS Was Manageable

	Treated Patients (N=47)			
	DL1 2.5×10^6 (N=4)	DL2 12.5×10^6 (N=30)	DL3 25×10^6 (N=7)	DL4 40×10^6 (N=6)
ICANS,[a] n (%)	0	**3 (10)**	0	2 (33)
Grade 1/2	0	**1 (3)**	0	2 (33)
Grade 3/4	0	**2 (7)**	0	0
Time to onset, days	–	**16 (10-28)[b]**	–	6, 28
Time from onset to resolution, days	–	**16 (11-24)[b]**	–	1, 25
Management of ICANS, n/N (%[c])				
Dexamethasone	–	**2/3 (67)**	–	1/2 (50)
Methylprednisolone	–	**1/3 (33)**	–	0
Anakinra	–	**1/3 (33)**	–	0

ASTCT, American Society for Transplantation and Cellular Therapy; DL, dose level; ICANS, immune effector cell-associated neurotoxicity syndrome.
[a]Per ASTCT 2019 criteria. ICANS adverse events are neurologic adverse events that occurred within 12 weeks post rapcabtagene autoleucel infusion in patients with ICANS grades 1-4. [b]Median (range).
[c]Percentage calculated based on the number of patients with ICANS.

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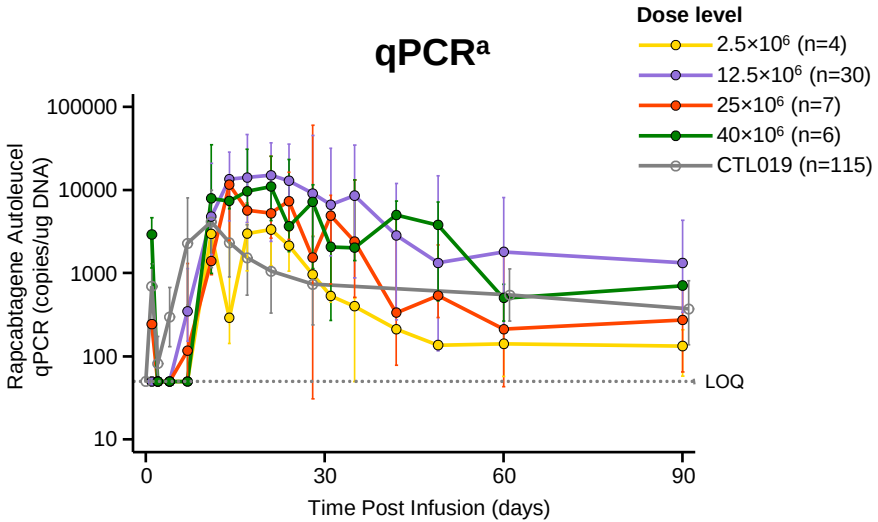
Rapcabtagene Autoleucel Expansion Was Robust

- At a 25-fold lower dose, rapcabtagene autoleucel expansion at DL2 by qPCR was at the higher end of tisagenlecleucel expansion in DLBCL[1,2]
- Rapcabtagene autoleucel kinetics measured by qPCR showed robust expansion at DL2 and no further increases at higher doses



DL, dose level; DLBCL, diffuse large B-cell lymphoma; LOQ, limit of quantification; qPCR, quantitative polymerase chain reaction.
[a]Median and IQR (interquartile range) over time measured by qPCR.
1. Awasthi R, et al. *Blood Adv*. 2020;4(3):560-572; 2. Schuster SJ, et al. *N Engl J Med*. 2019;380(1):45-56.

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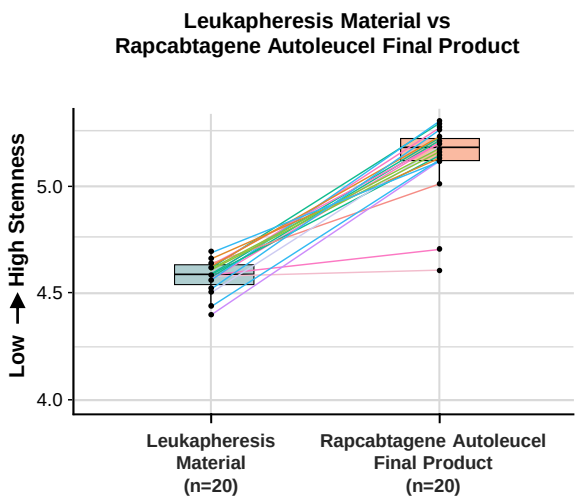
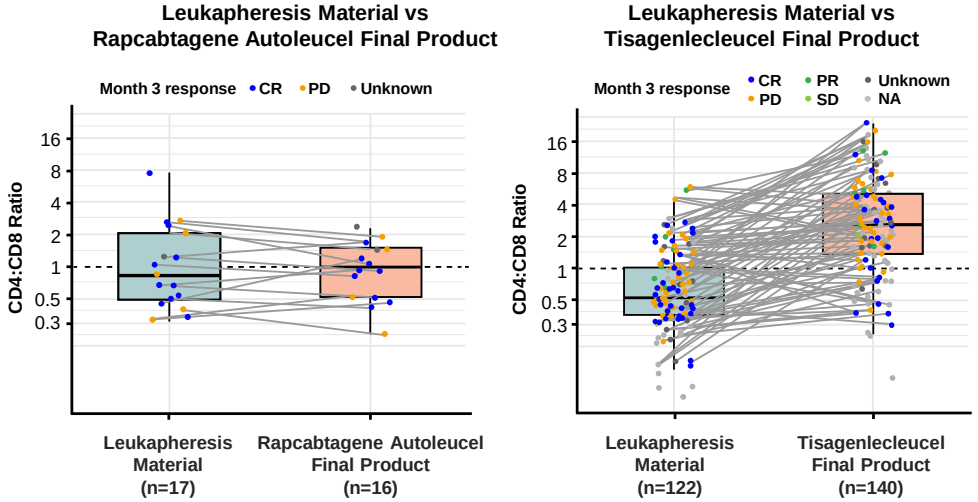
T-Charge™ Manufacturing Process Preserved T-Cell Stemness and CD4:CD8 Ratio in Rapcabtagene Autoleucel

Transcriptional Profile Analysis of Stemness



CD4:CD8 Ratio



CD, cluster of differentiation; CR, complete response; NA, not available; PD, progressive disease; PR, partial response; SD, stable disease.

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Conclusions

- Rapcabtagene autoleucel (YTB323) is a next-generation autologous CD19-directed CAR-T cell therapy that preserves T-cell stemness translating into the potential to deliver deep and more durable clinical responses and a favorable safety profile
- Rapcabtagene autoleucel (YTB323) is manufactured on a pioneering T-charge™ platform providing reliable and rapid manufacturing for your patients
- For further investigation in Phase II/III studies, the recommended dose is 12.5×106 CAR+ viable T cells (DL2), based on the CR rate, favorable safety profile, and cellular kinetics

CAR, chimeric antigen receptor; CD, cluster of differentiation; CR, complete response; DL, dose level.

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