A Global Phase 1B Study of JNJ-90014496, A CD19/CD20 Bispecific Chimeric Antigen Receptor T-Cell Therapy in Patients With Relapsed/Refractory Large B-Cell Lymphoma

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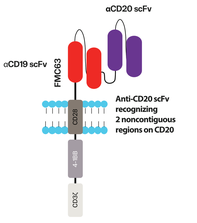
KEY TAKEAWAY

JNJ'4496 was shown to have a favorable safety and efficacy profile at the RP2D of 75M CAR+ T cells, with no high-grade CRS, minimal neurotoxicity, and high response rates, particularly in earlier lines of therapy. These results align with prior data on similar bispecific CAR T-cell therapies and support its continued development in R/R LBCL

INTRODUCTION

- CD19 chimeric antigen receptor (CAR) T-cell therapies have transformed treatment of relapsed/refractory (R/R) large B-cell lymphoma (LBCL), yet most patients do not have long-term remission[1-3]
- Dual targeting may protect against antigen escape as a potential resistance mechanism[4,5]
- C-CAR039 (**FIGURE 1**): 4-year follow-up from first-in-human study in China[6]
  - 1 grade 3 cytokine release syndrome (CRS); no grade 3 or 4 immune effector cell–associated neurotoxicity syndrome (ICANS)
  - Among patients with LBCL
    - Complete response (CR) rate was 86% (~50% remain in CR)
    - 4-year progression-free survival rate was 53%
    - 4-year overall survival rate was 67%

FIGURE 1: JNJ'4496 (formerly C-CAR039) targets both CD19 and CD20 antigens



CD; cluster of differentiation; scFv, single-chain variable fragment.

OBJECTIVE

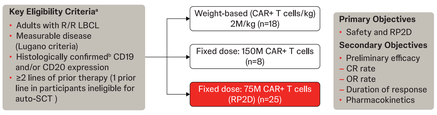
- To report initial results from the phase 1b study (NCT05421663) evaluating the efficacy and safety of JNJ'4496 in participants with R/R LBCL previously untreated with CAR T-cell therapy

METHODS

Study design

- NCT05421663 is a global, phase 1b study enrolling participants at 31 sites in 8 countries (**FIGURE 2**)
- Participants were offered bridging therapy at the investigator's discretion

FIGURE 2: Global phase 1b study design



auto-SCT, autologous stem cell transplant; CAR, chimeric antigen receptor; CD, cluster of differentiation; CR, complete response; LBCL, large B-cell lymphoma; M, million; OR, overall response; R/R, relapsed/refractory; RP2D, recommended phase 2 dose.
[a]Participants were screened, apheresed, and offered bridging therapy (at investigator's discretion); lymphodepletion of cyclophosphamide (300 mg/m^2/d) plus fludarabine (30 mg/m^2) was administered for 3 days.
[b]Histologically confirmed on the most recent post-relapse biopsy.

RESULTS

- At the data cut-off date, 51 heavily pretreated participants with R/R LBCL and no previous CAR T-cell treatment were infused with 2 million (M) CAR T cells/kg, n=18; 150M, n=8; and 75M, n=25
- 39% of participants had ≥2 prior lines of therapy and 67% had bridging therapy (**TABLE 1**)
- Median follow-up was 8 months

TABLE 1: Baseline characteristics of participants with R/R LBCL

Participant characteristics	All doses (N=51)	RP2D: 75M CAR+ T cells (n=25)
Age, median (range), years	72.0 (39–87)	72.0 (40–87)
Men, n (%)	35 (69)	19 (76)
DLBCL NOS,[a] n (%)	37 (73)	18 (72)
ECOG PS 1 or 2, n (%)	29 (57)	13 (52)
Number of prior lines of therapy, median (range)	1 (1–3)	2 (1–3)
1 prior line	31 (61)	12 (48)
≥2 prior lines	20 (39)	13 (52)
Primary refractory disease, n (%)	29 (57)	14 (56)
Prior bispecific antibodies, n (%)		
Anti-CD20[b]	5 (10)	5 (20)
Anti-CD19[c]	2 (4)	2 (8)
Bulky disease at baseline,[d] n (%)	13 (26)	8 (33)
IPI score of ≥3,[e,f] n/N (%)	14/49 (29)	6/24 (25)
Ann Arbor (stage III or IV),[e] n (%)	39 (76)	17 (68)
LDH at baseline > ULN, n (%)	18 (35)	9 (36)
Received bridging therapy, n (%)	34 (67)	14 (56)

CAR, chimeric antigen receptor; CD, cluster of differentiation; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; LBCL, large B-cell lymphoma; LDH, lactose dehydrogenase; M, million; NOS, not otherwise specified; R/R, relapsed/refractory; RP2D, recommended phase 2 dose; ULN, upper limit of normal.
[a]Other types of LBCL include transformed from a lower grade (all doses, n=6; 75M, n=4); high-grade B-cell lymphoma with *MYC*, *BCL2*, and/or *BCL6* rearrangements (all doses, n=5; 75M, n=2); and follicular lymphoma 3b and high-grade B-cell lymphoma not otherwise specified (n=1, each in all doses; none in the 75M group).
[b]Includes glofitamab and JNJ-87801493. [c]Includes R07227166 and RO7443904. [d]Bulky disease is defined as disease assessment including at least 1 lesion with longest diameter of >7 cm. [e]At screening. [f]No patients had an IPI of 4.

- Most common treatment-emergent adverse events were cytopenias and CRS (**TABLE 2**)
- 7 participants (28%) in the recommended phase 2 dose (RP2D) group reported serious treatment-emergent adverse events
- All 6 deaths on study were due to disease progression (RP2D cohort, n=3)

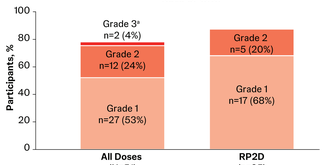
TABLE 2: Safety profile in R/R LBCL

TEAEs, n (%)	All doses (N=51)		RP2D (n=2)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any-grade TEAEs	51 (100)	44 (86)	25 (100)	21 (84)
Any-grade TEAEs reported in ≥20% of the all-doses group				
Neutropenia	43 (84)	40 (78)	19 (76)	18 (72)
CRS	41 (80)	2 (4)	22 (88)	0
Thrombocytopenia	24 (47)	10 (20)	11 (44)	3 (12)
Anemia	18 (35)	10 (20)	8 (32)	4 (16)
Fatigue	18 (35)	1 (2)	10 (40)	1 (4)
Diarrhea	15 (29)	1 (2)	9 (36)	1 (4)
Infections[a,b]	14 (27)	3 (6)	5 (20)	1 (4)
Leukopenia	12 (24)	11 (22)	4 (16)	3 (12)
Headache	10 (20)	0	3 (12)	0
Hypokalemia	10 (20)	0	5 (20)	0
Lymphopenia	10 (20)	6 (12)	5 (20)	4 (16)
Nausea	10 (20)	0	4 (16)	0

CRS, cytokine release syndrome; LBCL, large B-cell lymphoma; M, million; RP2D, recommended phase 2 dose; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event.
TEAEs are defined as adverse events occurring until day 90 post-administration of study drug or until start of subsequent anticancer therapy, whichever comes first.
[a]Grade 3/4 pneumonia (n=2) and peritonitis (n=1) were observed in the all-doses group (1 participant in the 75M group had grade 3 peritonitis).
[b]Grade 1/2 opportunistic infections (herpes zoster and oral candidiasis) were reported in 2 participants in the 75M group.

- At RP2D, no grade 3/4 CRS events occurred; most were grade 1 (**FIGURE 3**)
- No prophylactic tocilizumab or steroids were administered

FIGURE 3: CRS in R/R LBCL

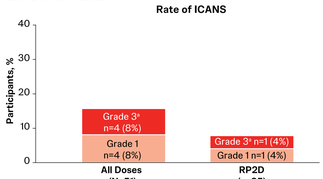


Participants	All doses (N=51)	RP2D (n=25)
Participants with CRS	41 (80)	22 (88)
Time to onset, median (range), days	3 (1–6)	3 (2–5)
Duration,[b] median (range), days	5 (1–13)	6 (1–12)
Supportive measures for CRS,[c] n (%)		
Tocilizumab	39 (76)	21 (84)
Corticosteroids	20 (39)	10 (40)
Oxygen	6 (12)	1 (4)
Vasopressor	2 (4)	0
Anakinra	1 (2)	0

CRS, cytokine release syndrome; LBCL, large B-cell lymphoma; M, million; R/R, relapsed/refractory; RP2D, recommended phase 2 dose.
[a]2 grade 3 CRSs were observed at the 150M dose: 1 CRS event resolved within 61 hours; the second CRS event improved to grade 2 within 24 hours.
[b]In case of multiple CRS events, the duration or time to recovery was calculated as the sum of the duration/time to recovery of the individual events.
[c]Participants may have received more than 1 supportive therapy. Treatments such as analgesics/anti-inflammatory agents, anti-infectives, and intravenous fluids were also administered.

- At all doses, ICANS resolved without sequelae
- At RP2D, few instances of ICANS were observed (**FIGURE 4**) and 1 grade 3 ICANS event improved to grade 1 after 40 hours of treatment (central nervous system lymphoma at study entry)
- No prophylactic tocilizumab or steroids were administered

FIGURE 4: ICANS in R/R LBCL

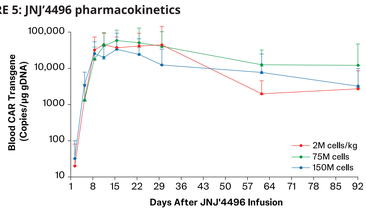


Participants	All doses (N=51)	RP2D (n=25)
Participants with ICANS, n (%)	8 (16)	2 (8)
Time to onset, median (range), days	3 (3–12)	3 (3–3)
Duration,[b] median (range), days	17 (1–89)	22 (17–26)
With concurrent CRS, n (%)	7 (14)	2 (8)
Supportive measures for ICANS,[c] n (%)		
Corticosteroids	8 (16)	2 (8)
Anakinra	5 (10)	2 (8)
Levetiracetam	3 (6)	2 (8)
Tocilizumab	2 (4)	0

CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome; LBCL, large B-cell lymphoma; R/R, relapsed/refractory; RP2D, recommended phase 2 dose.
[a]All grade 3 ICANS had a duration of ≤2 days.
[b]In case of multiple ICANS events, the duration/time to recovery was calculated as the sum of the duration/time to recovery of the individual events.
[c]Participants may have received more than 1 supportive therapy. Treatments such as intravenous fluids, antihistamines, pain medications, and antipsychotics were also administered.

- At RP2D (75M), CAR expansion and persistence were comparable to those observed at higher doses (**FIGURE 5**)
- At RP2D, median time at maximum observed concentration was noted to occur slightly later at 14 days post-infusion
- Efficacy was comparable across doses, which was supported by a consistent dose-response relationship for CR rate

FIGURE 5: JNJ'4496 pharmacokinetics

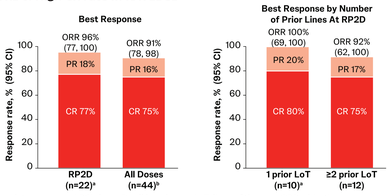


Pharmacokinetic parameter, unit	2M/kg (n=18)	150M (n=8)[a]	75M (n=22)
C_{max}, copies/µg gDNA	83,390 (106%)	52,152 (102%)	80,300 (102%)
$AUC_{0\text{-}29d}$, day x copies/µg gDNA	862,954 (91%)	515,465 (122%)	962,526 (102%)
t_{max}, median (min, max), day	12 (7, 28)	12 (7, 21)	14 (7, 28)

$AUC_{0\text{-}29d}$, area under the curve from day 0 to day 29; CAR, chimeric antigen receptor; C_{max}, maximum concentration; gDNA, genomic DNA; M, million; t_{max}, time at maximum observed concentration.
Reported as mean (% coefficient of variance) unless otherwise noted.
JNJ'4496 showed concordant cellular kinetic profiles by CAR transgene and CAR+ T-cell levels.
Pharmacokinetics sample cutoff date was February 28, 2025, with n=18 for 2M T-cells/kg, n=8 at 150M T-cell level, and n=22 for 75M T-cell level.
[a]n=7 for $AUC_{0\text{-}29d}$.

- At all doses and at RP2D, high CR rates were observed irrespective of number of lines of prior therapy (**FIGURE 6**)
- Response profiles are detailed in the **SUPPLEMENTARY FIGURE (QR Code)**

FIGURE 6: High CR rate in R/R LBCL



CR, complete response; LBCL, large B-cell lymphoma; LoT, lines of therapy; ORR, objective response rate; PR, partial response; R/R, relapsed/refractory; RP2D, recommended phase 2 dose.
Best response was assessed by investigators, based on Lugano criteria, using disease evaluations at any point in between the time of JNJ'4496 infusion until progressive disease or start of subsequent antilymphoma therapy, whichever occurred first.
[a]3 participants were not included in the efficacy analysis (2 participants achieved CR to bridging therapy and 1 participant was ongoing without any disease evaluations).
[b]7 participants were not included in the efficacy analysis (6 participants achieved CR to bridging therapy and 1 participant was ongoing without any disease evaluations).

CONCLUSIONS

Safety, efficacy, and pharmacokinetic profile support 75M CAR+ T cells as the RP2D of the CD19/CD20 CAR T-cell therapy, JNJ'4496, in a broad population of participant with R/R LBCL

At the RP2D
- No grade 3/4 CRS to date; 1 grade 3 ICANS lasting 40 hours in a participant with central nervous system lymphoma
- No prophylactic treatment for CRS or ICANS
- 100% ORR and 80% CR rates in participants who received 1 prior line of therapy; 75% CR rate in participants who received ≥2 prior lines of therapy

Findings are consistent with results shown for C-CAR039[6] and compare favorably to historical data with approved anti-CD19 CAR T-cell therapies[1-3]

These findings support further development of JNJ'4496 in R/R LBCL

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B-Cell Malignancies

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