Tolerability, efficacy, pharmacokinetics, and pharmacodynamics of BMS-986353 (CC-97540), a CD19-directed chimeric antigen receptor T cell therapy manufactured using a next-generation process, for severe, refractory autoimmune diseases: updated data from ongoing phase 1, multicenter, open-label studies

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Introduction

- Despite emergence of novel therapies in autoimmune diseases, there remains an unmet need for treatments that are effective in providing control or eliminating persistent disease activity to prevent accumulation of end-organ damage, with the potential for limited long-term treatment-related morbidity and mortality[1,2]
- One-time infusion of CD19-directed chimeric antigen receptor (CAR) T cell therapy in patients with treatment-resistant autoimmune diseases may reset their immune systems,[3] which may lead to durable, treatment-free remission in multiple B cell-driven diseases
- BMS-986353 (CC-97540) is an investigational CAR T cell therapy expressing the CD19-directing CAR construct used in the FDA-approved lisocabtagene maraleucel (liso-cel) (**Figure 1**)
- BMS-986353 is manufactured using the next-generation T cell (NEX-T®) process, which shortens manufacturing time and optimizes phenotypic attributes of the CAR T cell product[4] (**Figure 2**)
- Here, we report updated data on BMS-986353 in severe, refractory autoimmune diseases: systemic lupus erythematosus (SLE), idiopathic inflammatory myopathy (IIM), systemic sclerosis (SSc), and multiple sclerosis (MS)
  - Preliminary data are available for safety in all treated patients and for efficacy in patients with SLE[5]

Figure 1. CD19 NEX-T CAR construct

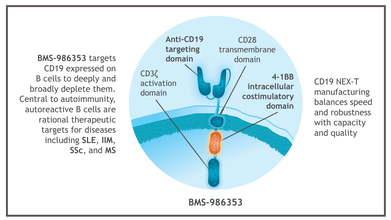
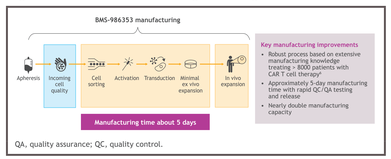


Figure 2. NEX-T manufacturing advantages

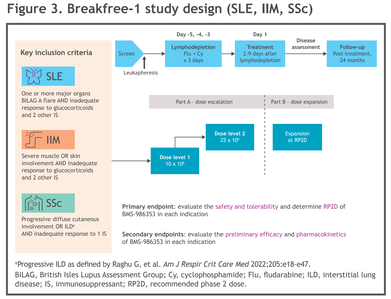


QA, quality assurance; QC, quality control.

Methods

- Two phase 1, multicenter, open-label studies are investigating BMS-986353 in patients with severe, refractory SLE, IIM, and SSc (Breakfree-1; NCT05869955), and relapsing or progressive forms of *MS* (Breakfree-2; NCT06220201) (**Figures 3** and **4**)
- Patients were treated with 5×10^8 (MS only), 10×10^8, or 25×10^8 CAR+ T cells according to dose level
- CAR T pharmacokinetics were evaluated using droplet digital polymerase chain reaction to detect transgene copy numbers, and pharmacodynamics were measured using flow cytometry

Figure 3. Breakfree-1 study design (SLE, IIM, SSc)



*Progressive ILD as defined by Raghu G, et al. *Am J Respir Crit Care Med* 2022;205:e18-e47.
BILAG, British Isles Lupus Assessment Group; Cy, cyclophosphamide; Flu, fludarabine; ILD, interstitial lung disease; IS, immunosuppressant; RP2D, recommended phase 2 dose.

- **In the basket trials of BMS-986353, a NEX-T investigational CD19-directed CAR T cell therapy (BMS-986353) showed manageable initial safety in patients with autoimmune diseases with a low incidence of low-grade CRS with a median duration of 2 days and no prolonged grade ≥ 3 cytopenias (Tables 2 and 3)**
- **All TEAEs of interest were brief and fully reversible**
  - **No grade 5 AEs occurred**
- **ICANS occurred in 2 patients in Breakfree-1, with a median duration of 3 days; there were no ICANS events reported for the 2 patients in Breakfree-2**
  - **Grade 3 ICANS was transient and resolved within 24 hours**

Table 2. Summary of TEAEs

TEAEs by indication, n (%)	Breakfree-1									Breakfree-2		
	SLE (n = 11)			SSc (n = 3)			IIM (n = 1)			RRMS (n = 2)		
	Any grade	≥ grade 3 unrelated	≥ grade 2 related	Any grade	≥ grade 3 unrelated	≥ grade 2 related	Any grade	≥ grade 3 unrelated	≥ grade 2 related	Any grade	≥ grade 3 unrelated	≥ grade 2 related
Any TEAE	11 (100.0)	9 (81.8)	6 (54.5)	3 (100.0)	1 (33.3)	3 (100.0)	1 (100.0)	1 (100.0)	1 (100.0)	2 (100.0)	1 (50.0)	0 (0)
Hematologic[a]												
Neutropenia	6 (54.5)	4 (36.4)	2 (18.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Anemia	5 (45.5)	1 (9.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (50.0)	0 (0)	0 (0)
Thrombocytopenia	3 (27.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
TEAEs of interest												
Infections	3 (27.3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Prolonged cytopenias[b]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Data cutoff for Breakfree-1: September 26, 2024. Data cutoff for Breakfree-2: September 24, 2024. Common Terminology Criteria for Adverse Events, version 5.0 is used for AE grading.
[a]Occurring in ≥ 10% of patients in any cohort or total population; neutrophil count decreased and lymphocyte count decreased are included in the overall hematologic TEAEs and are distinct terms from neutropenia and lymphopenia; [b]Grade 4 laboratory abnormalities of neutropenia, anemia, and/or thrombocytopenias lasting beyond day 42 after BMS-986353 infusion.

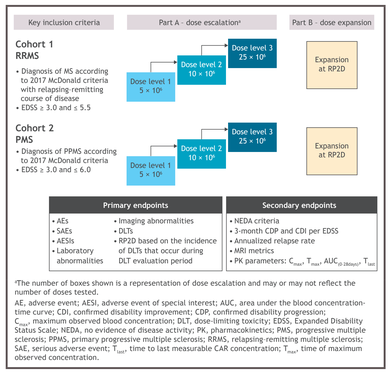
AE, adverse event; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome; NEX-T, next-generation T cell; IIM, idiopathic inflammatory myopathy; RRMS, relapsing-remitting multiple sclerosis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; TEAE, treatment-emergent adverse event.

Table 3. Summary of CRS and ICANS

CRS and ICANS	Breakfree-1 (n = 15)		Breakfree-2 (n = 2)	
	CRS	ICANS	CRS	ICANS
Any grade, n (%)	8 (53.3)	2 (13.3)	1 (50.0)	0 (0)
Grade 1	6 (40.0)	1 (6.7)	1 (50.0)	0 (0)
Grade 2	2 (13.3)	0 (0)	0 (0)	0 (0)
Grade ≥ 3	0 (0)	1 (6.7)	0 (0)	0 (0)
Median onset (range), days	7.5 (2-11)	9.0 (8-10)	9.0 (9-9)	0 (0)
Longest duration,[a] median (range), days	2.0 (1-5)	3.0 (3-3)	2.0 (2-2)	0 (0)
Treatment,[b] n (%)				
Tocilizumab	5 (33.3)	0 (0)	0 (0)	0 (0)
Dexamethasone	2 (13.3)	1 (6.7)	0 (0)	0 (0)
Anakinra	0 (0)	1 (6.7)	0 (0)	0 (0)

Common Terminology Criteria for Adverse Events, version 5.0 is used for AE grading except for CRS, which is graded based on Lee DW, et al. *Blood* 2014;124:188-195. ICANS symptoms include aphasia, confusion, altered mental status, seizures or seizure-like activity, and altered level of consciousness.
[a]Multiple events occurring within 7 days from each other are considered as 1 episode; [b]Data on common treatments were validated after data cutoff.

Figure 4. Breakfree-2 study design (MS)



[a]The number of boxes shown is a representation of dose escalation and may or may not reflect the number of doses tested.
AE, adverse event; AESI, adverse event of special interest; AUC, area under the blood concentration-time curve; CDI, confirmed disability improvement; CDP, confirmed disability progression; C_{max}, maximum observed blood concentration; DLT, dose-limiting toxicity; EDSS, Expanded Disability Status Scale; NEDA, no evidence of disease activity; PK, pharmacokinetics; PMS, progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; RRMS, relapsing-remitting multiple sclerosis; SAE, serious adverse event; T_{last}, time to last measurable CAR concentration; T_{max}, time of maximum observed concentration.

Results

Patient baseline disease characteristics

- As of September 26, 2024, 17 patients were treated with BMS-986353 (SLE, n = 11; SSc, n = 3; IIM, n = 1; RRMS, n = 2)
- Between both trials, at a median follow-up of 65.0 days (range, 3-316 days) in the Breakfree-1 trial and 71.5 days (range, 23-120 days) in the Breakfree-2 trial, 7 patients from the SLE cohort were evaluable for efficacy and 17 patients were evaluable for safety
- No patients discontinued study at data cutoff
- Baseline demographics and disease characteristics are shown in **Table 1**

Safety

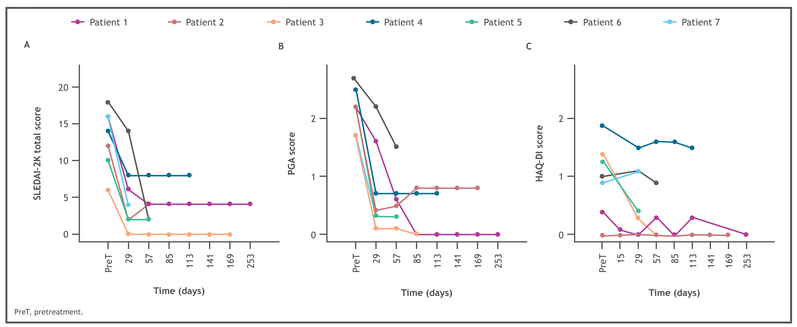
- Any-grade treatment-emergent adverse events (TEAEs) occurred in 11 patients with SLE, 3 patients with SSc, 1 patient with IIM, and 2 patients with MS (**Table 2**)
- Two patients experienced DLTs in Breakfree-1; there were no DLTs in Breakfree-2
- Any-grade cytokine release syndrome (CRS) occurred in 8 patients in Breakfree-1, with a median duration of 2 days. One patient with RRMS in Breakfree-2 experienced grade 1 CRS that lasted 1 day (**Table 3**)
- Immune effector cell-associated neurotoxicity syndrome (ICANS) was reported in 2 patients (grade 1 in a patient with SSc and grade 3 in a patient with SLE) in Breakfree-1, with a median duration of 3 days; there were no ICANS events reported for the 2 patients in Breakfree-2
  - Grade 3 ICANS symptoms were "waxing and waning mental status" and "decreased level of consciousness" and were transient and resolved on day 10 after cessation of confounding medications (oxycodone for pleuritic pain) and treatment with dexamethasone and anakinra
- In Breakfree-1, no patients experienced prolonged grade ≥ 3 cytopenias; there were no transient/reversible grade ≥ 3 neutropenias or thrombocytopenias in Breakfree-2 (**Table 2**)
- There were no prolonged cytopenias at > 29 days
- A 30-year-old female patient with a 16-year history of SLE became pregnant shortly after infusion. Following induction due to pre-eclampsia, uncomplicated vaginal delivery occurred at 37+1 weeks; newborn male had normal CD19+ B cell and CD3+ T cell numbers. Patient remains off all lupus-directed medications without evidence of new disease activity

Table 1. Baseline disease characteristics

	Breakfree-1			Breakfree-2
	Patients with SLE (n = 11)	Patients with SSc (n = 3)	Patients with IIM (n = 1)	Patients with RRMS (n = 2)
Median age (range), years	29.0 (18-49)	47.0 (43-55)	30.0 (30-30)	31.5 (30-33)
Female sex, n (%)	10 (90.1)	3 (100.0)	1 (100.0)	1 (50.0)
Race, n (%)				
White	4 (36.4)	2 (66.7)	1 (100.0)	2 (100.0)
Not reported/unknown	4 (36.4)	1 (33.3)	0 (0)	0 (0)
Black or African American	2 (18.2)	0 (0)	0 (0)	0 (0)
Asian	1 (9.1)	0 (0)	0 (0)	0 (0)
Median time from disease diagnosis to BMS-986353 infusion (range), years	7.3 (1.1-17.0)	1.2 (0.4-1.3)	3.6 (3.6-3.6)	7.8 (2.3-13.4)
Median number of prior therapies (range)	7.0 (3-10)	2.0 (2-5)	4.0 (4-4)	4.5 (1-8)
Median PGA score (range)[a]	2.0 (1.0-2.7)	6.5 (6.0-7.0)[b]	3.4 (3.4-3.4)	–
Median total SLEDAI-2K score (range)[c]	14.0 (0.0-18.0)	–	–	–
BILAG category A, n (%)				
Renal	9 (81.8)	–	–	–
Cardiorespiratory	2 (18.2)			
Median total mRSS (range)[d]	–	34.0 (14-42)	–	–
Median total MMT-8 (range)[e]	–	–	91.0 (91.0-91.0)	–
Median EDSS score (range)[a]	–	–	–	3.3 (3.0-3.5)

[a]Score scale: 1-10; [b]n = 2; [c]Score scale: 0-105; [d]Score scale: 0-51; [e]Score scale: 0-100.
MMT, Manual Muscle Testing; mRSS, modified Rodnan skin score; PGA, Physician's Global Assessment; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000.

Figure 5. SLE response assessments following treatment with BMS-986353



PreT, pretreatment.

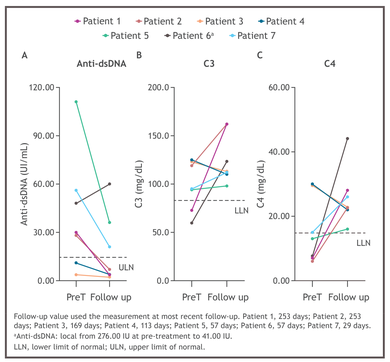
Efficacy in patients with SLE

- Three patients with SLE with at least 6 months of follow up remain off all therapies without evidence of new disease activity
- In all efficacy-evaluable patients, substantial improvements in SLEDAI-2K scores were observed for the SLE cohort (**Figure 5A**)
  - Median SLEDAI-2K score reduction of 10 points was observed at 1 month following BMS-986353 infusion
- PGA and HAQ-DI scores also improved substantially in efficacy-evaluable patients (**Figures 5B** and **5C**)
  - Median PGA score reduction of 82% was observed at 1 month following BMS-986353 infusion
  - Median HAQ-DI score reduction of 60% was observed at 1 month following BMS-986353 infusion
- One patient achieved Definitions of Remissions in SLE remission at 6 months
  - Two patients have persistent proteinuria. Confounding factors for residual proteinuria, including irreversible organ damage, are being explored

Biomarkers, PK, and pharmacodynamics in patients with SLE

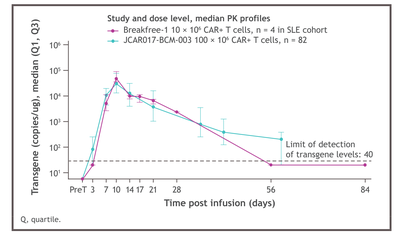
- For patients with abnormal biomarkers (anti-double-stranded [ds]DNA, C3, and C4), substantial improvement was achieved by day 29 in all treated patients with SLE (**Figure 6**)
- Robust CD19 NEX-T cell expansion at 10×10^8 (dose level 1) CAR+ T cells in patients with SLE is comparable to that at 10-fold higher approved dose of liso-cel (RP2D, 100×10^8 CAR+ T cells) in patients with non-Hodgkin lymphoma (**Figures 7** and **8A**)
  - In all patients, B cells became undetectable in the periphery by approximately 8 days post-BMS-986353 infusion
  - In patients with > 3 months of follow-up, B cells returned at a median of 113 days (range, 85-not reached)
- In patients with SLE, repopulating B cells were mainly naive, with few memory or CD11c+ atypical B cells, or plasmablasts (**Figure 8B**)

Figure 6. Anti-dsDNA, C3, and C4 in patients with SLE



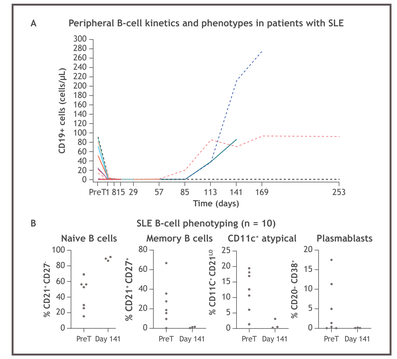
Follow-up value used the measurement at most recent follow-up. Patient 1, 253 days; Patient 2, 253 days; Patient 3, 169 days; Patient 4, 113 days; Patient 5, 57 days; Patient 6, 57 days; Patient 7, 29 days.
[a]Anti-dsDNA: local from 276.00 IU at pre-treatment to 41.00 IU.
LLN, lower limit of normal; ULN, upper limit of normal.

Figure 7. CAR T cell expansion compared with liso-cel



Q, quartile.

Figure 8. B-cell depletion and repopulation



Conclusions

- BMS-986353, a NEX-T investigational CD19-directed CAR T cell therapy, has a shortened manufacturing process, which is expected to decrease turnaround time, as well as optimized phenotypic attributes
- Across all dose levels, in patients with severe, refractory autoimmune diseases (SLE, SSc, IIM, and MS), BMS-986353 demonstrates a manageable safety profile with no unexpected AEs, with a low incidence of low-grade CRS and ICANS events
- All efficacy-evaluable patients with serious, highly refractory SLE remain off autoimmune-directed therapy without evidence of new disease activity at up to 11 months of follow-up
- Complete B-cell depletion and robust CAR T cell expansion comparable to liso-cel at RP2D is observed in all evaluable patients
  - Patients with B-cell reconstitution demonstrate a naive B-cell phenotype, consistent with hypothesis of immune reset
- Preliminary phase 1 data support favorable benefit-risk profile of BMS-986353 in patients with SLE and expansion into other autoimmune diseases. Dose escalation is ongoing to determine RP2D with optimal toxicity and efficacy profile in patients with autoimmune diseases
- Both studies continue to enroll patients in SLE, SSc, IIM, and MS indications

References

1. Campar A, et al. *Autoimmun Rev* 2011;10:685-692.
2. Winthrop KL, et al. *Ann Rheum Dis* 2020;79:88-93.
3. Müller F, et al. *N Engl J Med* 2024;390:687-700.
4. Costa LJ, et al. Oral presentation at the American Society of Hematology (ASH) Annual Meeting; December 10-13, 2022; New Orleans, LA, USA. Oral 566.
5. Schett G, et al. *Arthritis Rheumatol* 2024;76 (suppl 9):1753.
6. MarketWatch. https://www.marketwatch.com/story/bristol-myers-squibb-cell-therapy-gets-fda-green-light-to-treat-common-type-of-leukemia-b1f67779. Accessed October 29, 2024.

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